

**CO-ADMINISTRATION OF INTERLEUKIN-3 MUTANT POLYPEPTIDES  
WITH CSF'S FOR MULTI-LINEAGE HEMATOPOIETIC CELL  
PRODUCTION**

5                   Field of the Invention

          The present invention relates to the  
coadministration or sequential treatment using mutants  
or variants of human interleukin-3 (hIL-3) and other  
colony stimulating factors (CSFs), cytokines,  
10 lymphokines, interleukins, hematopoietic growth factors  
or IL-3 variants.

Background of the Invention

          Colony stimulating factors (CSFs) which stimulate  
15 the differentiation and/or proliferation of bone marrow  
cells have generated much interest because of their  
therapeutic potential for restoring depressed levels of  
hematopoietic stem cell-derived cells. CSFs in both  
human and murine systems have been identified and  
20 distinguished according to their activities. For  
example, granulocyte-CSF (G-CSF) and macrophage-CSF (M-  
CSF) stimulate the in vitro formation of neutrophilic  
granulocyte and macrophage colonies, respectively while  
GM-CSF and interleukin-3 (IL-3) have broader activities  
25 and stimulate the formation of both macrophage,  
neutrophilic and eosinophilic granulocyte colonies.  
IL-3 also stimulates the formation of mast,  
megakaryocyte and pure and mixed erythroid colonies  
(when erythropoietin is added).

30           Because of its ability to stimulate the  
proliferation of a number of different cell types and  
to support the growth and proliferation of progenitor  
cells, IL-3 has potential for therapeutic use in  
restoring hematopoietic cells to normal amounts in  
35 those cases where the number of cells has been reduced  
due to diseases or to therapeutic treatments such as  
radiation and/or chemotherapy.

Interleukin-3 (IL-3) is a hematopoietic growth factor which has the property of being able to promote the survival, growth and differentiation of

5 hematopoietic cells. Among the biological properties of IL-3 are the ability (a) to support the growth and differentiation of progenitor cells committed to all, or virtually all, blood cell lineages; (b) to interact with early multipotential stem cells; (c) to sustain

10 the growth of pluripotent precursor cells; (d) to stimulate proliferation of chronic myelogenous leukemia (CML) cells; (e) to stimulate proliferation of mast cells, eosinophils and basophils; (f) to stimulate DNA synthesis by human acute myelogenous leukemia (AML)

15 cells; (g) to prime cells for production of leukotrienes and histamines; (h) to induce leukocyte chemotaxis; and (i) to induce cell surface molecules needed for leukocyte adhesion.

Mature human interleukin-3 (hIL-3) consists of 133

20 amino acids. It has one disulfide bridge and two potential glycosylation sites (Yang, et al., CELL 47:3 (1986)).

Murine IL-3 (mIL-3) was first identified by Ihle, et al., J. IMMUNOL. 126:2184 (1981) as a factor which

25 induced expression of a T cell associated enzyme, 20'-hydroxysteroid dehydrogenase. The factor was purified to homogeneity and shown to regulate the growth and differentiation of numerous subclasses of early hematopoietic and lymphoid progenitor cells.

In 1984, cDNA clones coding for murine IL-3 were isolated (Fung, et al., NATURE 307:233 (1984) and Yokota, et al., PROC. NATL. ACAD. SCI. USA 81:1070 (1984)). The murine DNA sequence coded for a

30 polypeptide of 166 amino acids including a putative signal peptide.

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The gibbon IL-3 sequence was obtained using a gibbon cDNA expression library. The gibbon IL-3

sequence was then used as a probe against a human genomic library to obtain a human IL-3 sequence.

Gibbon and human genomic DNA homologues of the murine IL-3 sequence were disclosed by Yang, et al., CELL 47:3 (1986). The human sequence reported by Yang, et al. included a serine residue at position 8 of the mature protein sequence. Following this finding, others reported isolation of Pro<sup>8</sup> hIL-3 cDNAs having proline at position 8 of the protein sequence. Thus it appears that there may be two allelic forms of hIL-3.

Dorssers, et al., GENE 55:115 (1987), found a clone from a human cDNA library which hybridized with mIL-3. This hybridization was the result of the high degree of homology between the 3' noncoding regions of mIL-3 and hIL-3. This cDNA coded for an hIL-3 (Pro<sup>8</sup>) sequence.

U.S. 4,877,729 and U.S. 4,959,454 disclose human IL-3 and gibbon IL-3 cDNAs and the protein sequences for which they code. The hIL-3 disclosed has serine rather than proline at position 8 in the protein sequence.

Clark-Lewis, et al., SCIENCE 231:134 (1986) performed a functional analysis of murine IL-3 analogs synthesized with an automated peptide synthesizer. The authors concluded that the stable tertiary structure of the complete molecule was required for full activity. A study on the role of the disulfide bridges showed that replacement of all four cysteines by alanine gave a molecule with 1/500th the activity as the native molecule. Replacement of two of the four Cys residues by Ala(Cys79, Cys140 -> Ala79, Ala140) resulted in an increased activity. The authors concluded that in murine IL-3 a single disulfide bridge is required between cysteines 17 and 80 to get biological activity that approximates physiological levels and that this structure probably stabilizes the tertiary structure of the protein to give a conformation that is optimal for

function. (Clark-Lewis, et al., PROC. NATL. ACAD. SCI. USA 85:7897 (1988)).

International Patent Application (PCT) WO 88/00598 discloses gibbon- and human-like IL-3. The hIL-3  
5 contains a Ser<sup>8</sup> -> Pro<sup>8</sup> replacement. Suggestions are made to replace Cys by Ser, thereby breaking the disulfide bridge, and to replace one or more amino acids at the glycosylation sites.

EP-A-0275598 (WO 88/04691) illustrates that Ala<sup>1</sup>  
10 can be deleted while retaining biological activity. Some mutant hIL-3 sequences are provided, e.g., two double mutants, Ala<sup>1</sup> -> Asp<sup>1</sup>, Trp<sup>13</sup> -> Arg<sup>13</sup> (pGB/IL-302) and Ala<sup>1</sup> -> Asp<sup>1</sup>, Met<sup>3</sup> -> Thr<sup>3</sup> (pGB/IL-304) and one triple mutant Ala<sup>1</sup> -> Asp<sup>1</sup>, Leu<sup>9</sup> -> Pro<sup>9</sup>, Trp<sup>13</sup> ->  
15 Arg<sup>13</sup> (pGB/IL-303).

WO 88/05469 describes how deglycosylation mutants can be obtained and suggests mutants of Arg<sup>54</sup>Arg<sup>55</sup> and Arg<sup>108</sup>Arg<sup>109</sup>Lys<sup>110</sup> might avoid proteolysis upon  
expression in Saccharomyces cerevisiae by KEX2  
20 protease. No mutated proteins are disclosed. Glycosylation and the KEX2 protease activity are only important, in this context, upon expression in yeast.

WO 88/06161 mentions various mutants which theoretically may be conformationally and antigenically  
25 neutral. The only actually performed mutations are Met<sup>2</sup> -> Ile<sup>2</sup> and Ile<sup>131</sup> -> Leu<sup>131</sup>. It is not disclosed whether the contemplated neutralities were obtained for these two mutations.

WO 91/00350 discloses nonglycosylated hIL-3 analog  
30 proteins, for example, hIL-3 (Pro<sup>8</sup>Asp<sup>15</sup>Asp<sup>70</sup>), Met<sup>3</sup> rhuIL-3 (Pro<sup>8</sup>Asp<sup>15</sup>Asp<sup>70</sup>); Thr<sup>4</sup> rhuIL-3 (Pro<sup>8</sup>Asp<sup>15</sup>Asp<sup>70</sup>) and Thr<sup>6</sup> rhuIL-3 (Pro<sup>8</sup>Asp<sup>15</sup>Asp<sup>70</sup>). It is said that these protein compositions do not exhibit certain adverse side effects associated with native  
35 hIL-3 such as urticaria resulting from infiltration of mast cells and lymphocytes into the dermis. The disclosed analog hIL-3 proteins may have N termini at

Met<sup>3</sup>, Thr<sup>4</sup>, or Thr<sup>6</sup>.

WO 91/12874 discloses cysteine added variants (CAVs) of IL-3 which have at least one Cys residue substituted for a naturally occurring amino acid residue.

U.S. 4,810,643 discloses the DNA sequence encoding human G-CSF.

WO 91/07988 discloses a method to increase megakaryocyte production comprised of administration of G-CSF with IL-3 or GM-CSF. Also disclosed is a method for increasing platelet production comprised of administration of IL-6 with IL-3, G-CSF or GM-CSF.

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#### Summary of the Invention

The present invention encompasses recombinant human interleukin-3 (hIL-3) variant or mutant proteins (muteins). These hIL-3 muteins contain amino acid substitutions and may also have amino acid deletions at either/or both the N- and C- termini. This invention encompasses coadministration or sequential treatment using IL-3 variants of the present invention with other colony stimulating factors (CSFs), cytokines, lymphokines, interleukins, hematopoietic growth factors (herein after collectively referred to as "colony stimulating factors") which may have the potential for therapeutic use in restoring hematopoietic cells to normal amounts in those cases where the number of cells has been reduced due to diseases or to therapeutic treatments such as radiation and/or chemotherapy. Coadministration or sequential treatment using IL-3 variants of the present invention with other colony stimulating factors may enhance therapeutic value due to the synergistic effects of the proteins that make up the treatment. The use of multiple factors may also have the potential advantage by lowering the demands

placed on factor-producing cells and their induction systems. If there are limitations in the ability of a cell to produce a factor then by lowering the required concentrations of each of the factors by using them in combination may usefully reduce demands on the factor-producing cells. The use of multiple factors may lower the amount of the factors that would be needed, probably reducing the likelihood of adverse responses.

Coadministration or sequential treatment may have the usual activity of the peptides forming the mixture or it may be further characterized by having a biological or physiological activity greater than simply the additive function of the presence of IL-3 or the other growth factors alone. Coadministration or sequential treatment may also unexpectedly provide an enhanced effect on the activity or an activity different from that expected by the presence of IL-3 or the other growth factors. The IL-3 variants of the present invention may also have an improved activity profile which may include reduction of undesirable biological activities associated with native hIL-3.

The present invention includes mutants of hIL-3 in which from 1 to 14 amino acids have been deleted from the N-terminus and/or from 1 to 15 amino acids have been deleted from the C-terminus, containing multiple amino acid substitutions, which are used with other growth factors or IL-3 variant. Preferred IL-3 variants of the present invention include variants in which amino acids 1 to 14 have been deleted from the N-terminus, amino acids 126 to 133 have been deleted from the C-terminus and contain from about four to about twenty-six amino acid substitutions in the polypeptide sequence.

The present invention also provides IL-3 variants

which may function as IL-3 antagonists or as discrete antigenic fragments for the production of antibodies useful in immunoassay and immunotherapy protocols. Antagonists of hIL-3 would be particularly useful in blocking the growth of certain cancer cells like AML, CML and certain types of B lymphoid cancers. Other conditions where antagonists would be useful include those in which certain blood cells are produced at abnormally high numbers or are being activated by endogenous ligands. Antagonists would effectively compete for ligands, presumably naturally occurring hemopoietins including and not limited to IL-3, GM-CSF and IL-5, which might trigger or augment the growth of cancer cells by virtue of their ability to bind to the IL-3 receptor complex while intrinsic activation properties of the ligand are diminished. IL-3, GM-CSF and/or IL-5 also play a role in certain asthmatic responses. An antagonist of the IL-3 receptor may have the utility in this disease by blocking receptor-mediated activation and recruitment of inflammatory cells.

In addition to the use of the IL-3 variants of the present invention with other colony stimulating factors in vivo, it is envisioned that in vitro uses would include the ability to stimulate bone marrow and blood cell activation and growth before infusion into patients.

### 30 Brief Description of the Drawings

Figure 1 is the human IL-3 gene for E.coli expression (pMON5873), encoding the polypeptide sequence of natural (wild type) human IL-3 [SEQ ID NO:128], plus an initiator methionine, as expressed in E. coli, with the amino acids numbered from the N-terminus of the natural hIL-3.

Figure 2 shows the synergistic effects, in the methylcellulose assay, of the IL-3 variant, pMON13288, with G-CSF compared to the synergy of native IL-3 with G-CSF . Also shown are the effects of native IL-3 and the IL-3 variant, pMON13288, alone. The concentration of IL-3 is plotted versus the colony counts per 100,000 starting CD34+ cells.

Figure 3 shows the synergistic effects, in the methylcellulose assay, of the IL-3 variant, pMON13288, with GM-CSF compared to the synergy of native IL-3 with GM-CSF . Also shown are the effects of native IL-3 and the IL-3 variant, pMON13288, alone. The concentration of IL-3 is plotted versus the colony counts per 100,000 starting CD34+ cells.

Figure 4 shows the synergistic effects, in the cord blood assay, of the IL-3 variant, pMON13288, with stem cell factor (SCF) compared to the synergy of native IL-3 (pMON5873) with stem cell factor (SCF). Also shown are the effects of native IL-3 (pMON5873) and the IL-3 variant, pMON13288, alone. The concentration of IL-3 is plotted versus the colony counts (CFU) per 10,000 starting CD34+ cells.

Figure 5 shows the synergistic effects, in the cord blood assay, of the IL-3 variant, pMON13288, with stem cell factor (SCF) compared to the synergy of native IL-3 (pMON5873) with stem cell factor (SCF). Also shown are the effects of native IL-3 (pMON5873) and the IL-3 variant, pMON13288, alone. The concentration of IL-3 is plotted versus the colony counts (CFU) per 10,000 starting CD34+ cells.



The present invention encompasses the coadministration or sequential treatment with recombinant human interleukin-3 (hIL-3) variant or mutant proteins (muteins) with other colony stimulating factors (CSFs), cytokines, lymphokines, interleukins, hematopoietic growth factors and variants thereof (herein after collectively referred to as "colony stimulating factors"). This invention encompasses the coadministration or sequential treatment using IL-3 variants and other colony stimulating factors colony stimulating factors, each of which may act through a different and specific cell receptor to initiate complementary biological activities. Hematopoiesis requires a complex series of cellular events in which stem cells generate continuously into large populations of maturing cells in all major lineages. There are currently at least 20 known regulators with hematopoietic proliferative activity. Most of these proliferative regulators can stimulate one or another type of colony formation in vitro, the precise pattern of colony formation stimulated by each regulator is quite distinctive. No two regulators stimulate exactly the same pattern of colony formation, as evaluated by colony numbers or, more importantly, by the lineage and maturation pattern of the cells making up the developing colonies. Proliferative responses can most readily be analyzed in simplified in vitro culture systems. Three quite different parameters can be distinguished: alteration in colony size, alteration in colony numbers and cell lineage. Two or more factors may act on the progenitor cell, inducing the formation of larger number of progeny thereby increasing the colony size. Two or more factors may allow increased number of progenitor cells to proliferate either because distinct subsets of progenitors cells exist that respond exclusively to one factor or because some progenitors require stimulation by two or more factors

before being able to respond. Activation of additional receptors on a cell by the use of two or more factors is likely to enhance the mitotic signal because of coalescence of initially differing signal pathways into a common final pathway reaching the nucleus (Metcalf, 1989). Other mechanism could explain synergy. For example, if one signaling pathway is limited by an intermediate activation of an additional signaling pathway by a second factor may result in a superadditive response. In some cases, activation of one receptor type can induce an enhanced expression of other receptors (Metcalf, 1993). Two or more factors may result in a different pattern of cell lineages then from a single factor. The use of the IL-3 variants of the present invention with other colony stimulating factors may have the potential clinical advantage resulting from a proliferative response that is not possible by any single factor.

Hematopoietic and other growth factors can be grouped in to two distinct families of related receptors: (1) tyrosine kinase receptors, including those for epidermal growth factor, M-CSF (Sherr, 1990) and SCF (Yarden et al., 1987): and (2) hematopoietic receptors, not containing a tyrosine kinase domain, but exhibiting obvious homology in their extracellular domain (Bazan, 1990). Included in the later group are erythropoietin (D'Andrea et al., 1989), GM-CSF (Gearing et al., 1989), IL-3 (Kitamura et al., 1991), G-CSF (Fukunaga et al., 1990), IL-4 (Harada et al., 1990), IL-5 (Takaki et al., 1990), IL-6 (Yamasaki et al., 1988), IL-7 (Goodwin et al., 1990), LIF (Gearing et al., 1991) and IL-2 (Cosman et al., 1987). Most of the later group of receptors exists in high-affinity form as a heterodimers. After ligand binding, the specific  $\alpha$ -chains become associated with at least one other receptor chain ( $\beta$ -chain,  $\gamma$ -chain). Many of these factors share a common receptor

subunit. The  $\alpha$ -chains for GM-CSF, IL-3 and IL-5 share the same  $\beta$ -chain (Kitamura et al., 1991) and receptor complexes for IL-6, LIF and IL-11 share a common  $\beta$ -chain (gp130) (Taga et al., 1989; Gearing et al., 1992). The receptor complexes of IL-2, IL-4 and IL-7 share a common  $\gamma$ -chain (Kondo et al., 1993; Russell et al., 1993; Noguchi et al., 1993).

GM-CSF accelerates recovery of neutrophils and maintains functional capacity, yet has little demonstrable effect on platelet recovery. In contrast IL-3 promotes a slower increase recovery in neutrophils and monocytes while accelerating the recovery of platelets.

Recent studies in normal primates indicate that when IL-3 was administered before GM-CSF that the combination of IL-3 and GM-CSF promoted a synergistic rise in peripheral white blood cells and platelets (Donahue R. E. et al., 1988; Krumwieh D. et al., 1988; and Stahl C.P. et al., 1992). The synergistic effect observed in the sequential combination of IL-3 before GM-CSF may result from the expansion of GM-CSF sensitive cells by IL-3 resulting in a more efficient production of neutrophils. The coadministration of GM-CSF and IL-3 resulted in diminished neutrophils production relative to GM-CSF alone (Farese et al., 1993). The coadministration of IL-3 and GM-CSF, may result in down regulation of GM-CSF receptors by IL-3 thereby dampening the GM-CSF induced increase in neutrophils. However the coadministration of IL-3 and GM-CSF in a marrow-ablated rhesus monkeys promoted accelerated platelets and neutrophil recovery relative to sequential cytokine treatment or with either IL-3 or GM-CSF alone (Farese et al., 1993).

The in vitro activity of both IL-3 and GM-CSF has

been shown to be additive with respect to stimulating larger colonies than either cytokine alone (Robinson et al., 1987; Bruno et al., 1989; Metcalf et al., 1992; Bruno et al., 1991; Bridell et al., 1990). Recently  
5 IL-12 has been shown to synergize with IL-3 and c-kit (stem cell factor) to enhance the recovery of hemopoietic stem cells in liquid culture (Ploemacher et al., 1993).

10 Recent in vitro (Emerson et al., 1988; Sonodo et al., 1988) and in vivo (Ganser et al., 1992; Donahue R. E. et al., 1988; Krumwieh D. et al., 1988; and Stahl C.P. et al., 1992) results of combined IL-3 and GM-CSF treatment suggests an increased clinical efficacy in  
15 cytokine combination treatment.

As mentioned earlier some of the factors that are involved in hematopoiesis are limited to a specific cell lineage and others have much broader effects and  
20 may result in the proliferation and support of multilineages and there may be considerable overlap between these factors but that the proliferative profiles are distinct. This suggests that the coadministration or sequential treatment with multiple factors may have a  
25 clinical advantage. IL-3 variants of the present invention that have an increased therapeutic index, compared to native IL-3, may have a distinct clinical advantage when coadministered or used sequentially in treatment.

30 The use of multiple factors may also have potential advantage by lowering the demands placed on factor-producing cells and their induction systems. If there are limitations in the ability of a cell to produce a factor then by lowering the required  
35 concentrations of each of the factors by using them in combination may usefully reduce demands on the factor-producing cells. The use of multiple factors may lower

the amount of the factors that would be needed,  
probably reducing the likelihood of adverse responses.

A non-exclusive list of growth factors, colony  
5 stimulating factors (CSFs) including; cytokines,  
lymphokines, interleukins, hematopoietic growth  
factors, which can be used in coadministration or  
sequential treatment with the hIL-3 variant of the  
present invention include GM-CSF, CSF-1, G-CSF, Meg-CSF  
10 (more recently referred to as c-mpl ligand), M-CSF,  
erythropoietin (EPO), IL-1, IL-4, IL-2, IL-5, IL-6, IL-  
7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, LIF,  
flt3/flk2, human growth hormone, B-cell growth factor,  
B-cell differentiation factor, eosinophil  
15 differentiation factor and stem cell factor (SCF) also  
known as steel factor or c-kit ligand and variants  
thereof.

The present invention relates to novel variants of  
20 human interleukin-3 (hIL-3) in which amino acid  
substitutions have been made at four or more positions  
in amino acid sequence of the polypeptide used in  
sequential treatment or coadministration with other  
colony stimulating factors. Preferred IL-3 variants of  
25 the present invention which have deletions of amino  
acids 1 to 14 at the N-terminus and 126 to 133 at the  
C-terminus and which also have four or more amino acid  
substitutions in the polypeptide used in coadministered  
or sequential treatment with other colony stimulating  
30 factors or IL-3 variants. Among the preferred IL-3  
variants are those having twenty-six amino acid  
substitutions. The present invention includes mutant  
polypeptides comprising minimally amino acids 15 to 118  
of hIL-3 with or without additional amino acid  
35 extensions to the N-terminus and/or C-terminus which  
further contain four or more amino acid substitutions  
in the amino acid sequence of the polypeptide.

As used herein human interleukin-3 corresponds to the amino acid sequence (1-133) as depicted in Figure 1 and (15-125) hIL-3 corresponds to the 15 to 125 amino acid sequence of the hIL-3 polypeptide. Naturally occurring variants of hIL-3 polypeptide amino acids are also included in the present invention (for example, the allele in which proline rather than serine is at position 8 in the hIL-3 polypeptide sequence) as are variant hIL-3 molecules which are modified post-translationally (e.g. glycosylation).

"Mutant amino acid sequence," "mutant protein" or "mutant polypeptide" refers to a polypeptide having an amino acid sequence which varies from a native sequence or is encoded by a nucleotide sequence intentionally made variant from a native sequence. "Mutant protein," "variant protein" or "mutein" means a protein comprising a mutant amino acid sequence and includes polypeptides which differ from the amino acid sequence of native hIL-3 due to amino acid deletions, substitutions, or both. "Native sequence" refers to an amino acid or nucleic acid sequence which is identical to a wild-type or native form of a gene or protein.

Human IL-3 can be characterized by its ability to stimulate colony formation by human hematopoietic progenitor cells. The colonies formed include erythroid, granulocyte, megakaryocyte, granulocytic macrophages and mixtures thereof. Human IL-3 has demonstrated an ability to restore bone marrow function and peripheral blood cell populations to therapeutically beneficial levels in studies performed initially in primates and subsequently in humans (Gillio, A. P., et al. (1990); Ganser, A, et al. (1990); Falk, S., et al. (1991). Additional activities of hIL-3 include the ability to stimulate leukocyte

migration and chemotaxis; the ability to prime human leukocytes to produce high levels of inflammatory mediators like leukotrienes and histamine; the ability to induce cell surface expression of molecules needed for leukocyte adhesion; and the ability to trigger dermal inflammatory responses and fever. Many or all of these biological activities of hIL-3 involve signal transduction and high affinity receptor binding. Coadministration or sequential treatment using the IL-3 variants of the present invention with other colony stimulating factors may exhibit useful properties such as having similar or greater biological activity when compared to native hIL-3 or by having improved half-life or decreased adverse side effects, or a combination of these properties. The IL-3 variants of the present invention may also be useful as antagonists. IL-3 variants which have little or no activity when compared to native hIL-3 may still be useful as antagonists, as antigens for the production of antibodies for use in immunology or immunotherapy, as genetic probes or as intermediates used to construct other useful hIL-3 muteins.

The use of IL-3 variants of the present invention when coadministered or as part of sequential treatment will preferably have at least one biological property of human IL-3. Coadministration or sequential treatment may also have more than one IL-3-like biological property, or an improved property, or a reduction in an undesirable biological property of human IL-3. Some mutant polypeptides of the present invention may also exhibit an improved side effect profile. For example, they may exhibit a decrease in leukotriene release or histamine release when compared to native hIL-3 or (15-125) hIL-3. Such hIL-3 or hIL-3-like biological properties may include one or more of the following biological characteristics and in vivo and in vitro activities.

One such property is the support of the growth and differentiation of progenitor cells committed to erythroid, lymphoid, and myeloid lineages. For example, in a standard human bone marrow assay, an IL-3-like biological property is the stimulation of granulocytic type colonies, megakaryocytic type colonies, monocyte/macrophage type colonies, and erythroid bursts. Other IL-3-like properties are the interaction with early multipotential stem cells, the sustaining of the growth of pluripotent precursor cells, the ability to stimulate chronic myelogenous leukemia (CML) cell proliferation, the stimulation of proliferation of mast cells, the ability to support the growth of various factor-dependent cell lines, and the ability to trigger immature bone marrow cell progenitors. Other biological properties of IL-3 have been disclosed in the art. Human IL-3 also has some biological activities which may in some cases be undesirable, for example the ability to stimulate leukotriene release and the ability to stimulate increased histamine synthesis in spleen and bone marrow cultures and in vivo.

Biological activity of hIL-3 and hIL-3 variant proteins of the present invention is determined by DNA synthesis by human acute myelogenous leukemia cells (AML). The factor-dependent cell line AML 193 was adapted for use in testing biological activity. The biological activity of hIL-3 and hIL-3 variant proteins of the present invention is also determined by counting the colony forming units in a bone marrow assay.

Other in vitro cell based assays may also be useful to determine the synergistic effect of multiple colony stimulating factors that comprise the mixture. The following are examples of other useful assays.

TF-1 proliferation assay: The TF-1 cell line was



- derived from bone marrow of a patient with erythroleukemia (Kitamura et al., 1989). TF-1 cells respond to IL-3, GM-CSF, EPO and IL-5. 32D proliferation assay: 32D is a murine IL-3 dependent cell line which does not respond to human IL-3 but does respond to human G-CSF which is not species restricted. T1165 proliferation assay: T1165 cells are a IL-6 dependent murine cell line (Nordan et al., 1986) which respond to IL-6 and IL-11. Human Plasma Clot meg-CSF Assay: Used to assay megakaryocyte colony formation activity (Mazur et al., 1981).
- One object of the present invention is to provide hIL-3 variant with four or more amino acid substitutions in the polypeptide sequence used in coadministration or sequential treatment with other colony stimulating factors or IL-3 variants, which have similar or improved biological activity in relation to native hIL-3 or the other colony stimulating factors or IL-3 variant.
- The hIL-3 variants of the present invention may have hIL-3 or hIL-3-like activity. For example, they may possess one or more of the biological activities of native hIL-3 and may be useful in stimulating the production of hematopoietic cells by human or primate progenitor cells. The IL-3 variants of the present invention and pharmaceutical compositions containing them may be useful in the treatment of conditions in which hematopoietic cell populations have been reduced or destroyed due to disease or to treatments such as radiation or chemotherapy. Pharmaceutical compositions containing IL-3 variants of the present invention can be administered parenterally, intravenously, or subcutaneously.

Native hIL-3 possesses considerable inflammatory activity and has been shown to stimulate synthesis of the arachidonic acid metabolites LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub>; histamine synthesis and histamine release. Human  
5 clinical trials with native hIL-3 have documented inflammatory responses (Biesma, et al., BLOOD, 80:1141-1148 (1992) and Postmus, et al., J. CLIN. ONCOL., 10:1131-1140 (1992)). A recent study indicates that leukotrienes were involved in IL-3 actions in vivo and  
10 may contribute significantly to the biological effects of IL-3 treatment (Denzlinger, C., et al., BLOOD, 81:2466-2470 (1993))

Some IL-3 variants of the present invention, when co-administered with other CSFs, cytokines,  
15 lymphokines, interleukins, hematopoietic growth factors or IL-3 variants, may have an improved therapeutic profile as compared to native hIL-3 or (15-125)hIL-3. For example, some IL-3 variants of the present invention may have a similar or more potent growth  
20 factor activity relative to native hIL-3 or (15-125)hIL-3 without having a similar or corresponding increase in the stimulation of leukotriene or histamine. These IL-3 variants would be expected to have a more favorable therapeutic profile since the  
25 amount of polypeptide which needs to be given to achieve the desired growth factor activity (e.g. cell proliferation) would have a diminished leukotriene or histamine stimulating effect. In studies with native hIL-3, the stimulation of inflammatory factors has been  
30 an undesirable side effect of the treatment. Reduction or elimination of the stimulation of mediators of inflammation would provide an advantage over the use of native hIL-3.

Novel IL-3 variants of the present invention may  
35 also be useful as antagonists which block the hIL-3 receptor by binding specifically to it and preventing binding of the agonist.

One potential advantage of the novel IL-3 variants of the present invention, particularly those which retain activity similar to or better than that of native hIL-3, is that it may be possible to use a smaller amount of the biologically active mutein to produce the desired therapeutic effect. This may make it possible to reduce the number of treatments necessary to produce the desired therapeutic effect. The use of smaller amounts may also reduce the possibility of any potential antigenic effects or other possible undesirable side effects. For example, if a desired therapeutic effect can be achieved with a smaller amount of polypeptide it may be possible to reduce or eliminate side effects associated with the administration of native IL-3 such as the stimulation of leukotriene and/or histamine release. The novel IL-3 variants of the present invention may also be useful in the activation of stem cells or progenitors which have low receptor numbers.

Compounds of this invention are preferably made by genetic engineering techniques now standard in the art United States Patent 4,935,233 and Sambrook et al., "Molecular Cloning. A Laboratory Manual", Cold Spring Harbor Laboratory (1989)]. One method of creating the preferred hIL-3 (15-125) mutant genes is cassette mutagenesis [Wells, et al. (1985)] in which a portion of the coding sequence of hIL-3 in a plasmid is replaced with synthetic oligonucleotides that encode the desired amino acid substitutions in a portion of the gene between two restriction sites. In a similar manner amino acid substitutions could be made in the full-length hIL-3 gene, or genes encoding variants of hIL-3 in which from 1 to 14 amino acids have been deleted from the N-terminus and/or from 1 to 15 amino acids have been deleted from the C-terminus. When properly assembled these oligonucleotides would encode

hIL-3 variants with the desired amino acid substitutions and/or deletions from the N-terminus and/or C-terminus. These and other mutations could be created by those skilled in the art by other  
5 mutagenesis methods including; oligonucleotide-directed mutagenesis [Zoller and Smith (1982, 1983, 1984), Smith (1985), Kunkel (1985), Taylor, et al. (1985), Deng and Nickoloff (1992)] or polymerase chain reaction (PCR) techniques [Saiki, (1985)].

10

Plasmid DNA can be treated with the chosen restriction endonucleases then ligated to the annealed oligonucleotides. The ligated mixtures can be used to transform competent JM101 cells to resistance to an  
15 appropriate antibiotic. Single colonies can be picked and the plasmid DNA examined by restriction analysis and/or DNA sequencing to identify plasmids with mutant hIL-3 genes.

20

Suitable cells or cell lines for the production of the proteins claimed in the present invention may be bacterial cells. For example, the various strains of E. coli are well-known as host cells in the field of biotechnology. Examples of such strains include E. coli strains JM101 [Yanish-Perron, et al. (1985)] and  
25 MON105 [Obukowicz, et al. (1992)]. Also included in the present invention is the expression of the IL-3 variant protein utilizing a chromosomal expression vector for E. coli based on the bacteriophage Mu (Weinberg et al., 1993). Various strains of E. subtilis may also be employed as host cells for  
30 expression of the polypeptides of the present invention. Many strains of yeast cells known to those skilled in the art are also available as host cells for expression of the polypeptides of the present  
35 invention. When expressed in the E. coli cytoplasm, the above-mentioned mutant hIL-3 variants of the

present invention may also be constructed with Met-Ala- at the N-terminus so that upon expression the Met is cleaved off leaving Ala at the N-terminus. The IL-3 variant proteins of the present invention may include

5 polypeptides having Met-, Ala- or Met-Ala- attached to the N-terminus. When the IL-3 variant polypeptides are expressed in the cytoplasm of E. coli, polypeptides with and without Met attached to the N-terminus are obtained. The N-termini of proteins made in the

10 cytoplasm of E. coli are affected by posttranslational processing by methionine aminopeptidase (Ben-Bassat et al., 1987) and possibly by other peptidases. These IL-3 variant proteins may also be expressed in E. coli by fusing a signal peptide to the N-terminus. This signal

15 peptide is cleaved from the polypeptide as part of the secretion process. Secretion in E. coli can be used to obtain the correct amino acid at the N-terminus (e.g., Asn<sup>15</sup> in the (15-125) hIL-3 polypeptide) due to the precise nature of the signal peptidase. This is in

20 contrast to the heterogeneity which may be observed at the N-terminus of proteins expressed in the cytoplasm in E. coli.

Also suitable for use in the present invention are

25 mammalian cells, such as Chinese hamster ovary cells (CHO). General methods for expression of foreign genes in mammalian cells are reviewed in: Kaufman, R. J. (1987) High level production of proteins in mammalian cells, in Genetic Engineering, Principles and Methods,

30 Vol. 9, J. K. Setlow, editor, Plenum Press, New York. An expression vector is constructed in which a strong promoter capable of functioning in mammalian cells drives transcription of a eukaryotic secretion signal peptide coding region, which is translationally fused

35 to the coding region for the IL-3 variant. For example, plasmids such as pCDNA I/Neo, pRc/RSV, and pRc/CMV (obtained from Invitrogen Corp., San Diego,

California) can be used. The eukaryotic secretion signal peptide coding region can be from the hIL-3 gene itself or it can be from another secreted mammalian protein (Bayne, M. L. et al. (1987) Proc. Natl. Acad. Sci. USA 84, 2638-2642). After construction of the vector containing the hIL-3 variant gene, the vector DNA is transfected into mammalian cells. Such cells can be, for example, the COS7, HeLa, BHK, CHO, or mouse L lines. The cells can be cultured, for example, in DMEM media (JRH Scientific). The hIL-3 variant secreted into the media can be recovered by standard biochemical approaches following transient expression 24 - 72 hours after transfection of the cells or after establishment of stable cell lines following selection for neomycin resistance. The selection of suitable mammalian host cells and methods for transformation, culture, amplification, screening and product production and purification are known in the art. See, e.g., Gething and Sambrook, Nature, 293:620-625 (1981), or alternatively, Kaufman et al, Mol. Cell. Biol., 5(7):1750-1759 (1985) or Howley et al., U.S. Pat. No. 4,419,446. Another suitable mammalian cell line is the monkey COS-1 cell line. A similarly useful mammalian cell line is the CV-1 cell line.

Where desired, insect cells may be utilized as host cells in the method of the present invention. See, e.g. Miller et al, Genetic Engineering, 8:277-298 (Plenum Press 1986) and references cited therein. In addition, general methods for expression of foreign genes in insect cells using Baculovirus vectors are described in: Summers, M. D. and Smith, G. E. (1987) - A manual of methods for Baculovirus vectors and insect cell culture procedures, Texas Agricultural Experiment Station Bulletin No. 1555. An expression vector is constructed comprising a Baculovirus transfer vector, in which a strong Baculovirus promoter (such as the polyhedron promoter) drives transcription of a

eukaryotic secretion signal peptide coding region, which is translationally fused to the coding region for the IL-3 variant polypeptide. For example, the plasmid pVL1392 (obtained from Invitrogen Corp., San Diego, California) can be used. After construction of the vector carrying the gene encoding the IL-3 variant polypeptide, two micrograms of this DNA is cotransfected with one microgram of Baculovirus DNA (see Summers & Smith, 1987) into insect cells, strain SF9. Pure recombinant Baculovirus carrying the IL-3 variant gene is used to infect cells cultured, for example, in Excell 401 serum-free medium (JRH Biosciences, Lenexa, Kansas). The IL-3 variant protein secreted into the medium can be recovered by standard biochemical approaches. Supernatants from mammalian or insect cells expressing the IL-3 variant protein can be first concentrated using any of a number of commercial concentration units.

Coadministration or sequential treatment using IL-3 variants of the present invention with other colony stimulating factors may be useful in the treatment of diseases characterized by a decreased levels of either myeloid, erythroid, lymphoid, or megakaryocyte cells of the hematopoietic system or combinations thereof. In addition, they may be used to activate mature myeloid and/or lymphoid cells. Among conditions susceptible to treatment with the polypeptides of the present invention is leukopenia, a reduction in the number of circulating leukocytes (white cells) in the peripheral blood. Leukopenia may be induced by exposure to certain viruses or to radiation. It is often a side effect of various forms of cancer therapy, e.g., exposure to chemotherapeutic drugs, radiation and of infection or hemorrhage. Therapeutic treatment of leukopenia with these IL-3 variants of the present invention with other colony stimulating factors may

avoid undesirable side effects caused by treatment with presently available drugs.

Coadministration or sequential treatment using IL-3 variants of the present invention with other colony stimulating factors may be useful in the treatment of neutropenia and, for example, in the treatment of such conditions as aplastic anemia, cyclic neutropenia, idiopathic neutropenia, Chediak-Higashi syndrome, systemic lupus erythematosus (SLE), leukemia, myelodysplastic syndrome and myelofibrosis.

The IL-3 variants of the present invention, when coadministered or used in sequential treatment with other colony stimulating factors, may be useful in the treatment or prevention of thrombocytopenia. Currently the only therapy for thrombocytopenia is platelet transfusions which are costly and carry the significant risks of infection (HIV, HBV) and alloimmunization. The IL-3 variants, when coadministered or used in sequential treatment with other colony stimulating factors, may alleviate or diminish the need for platelet transfusions. Severe thrombocytopenia may result from genetic defects such as Fanconi's Anemia, Wiscott-Aldrich, or May-Hegglin syndromes. Acquired thrombocytopenia may result from auto- or allo-antibodies as in Immune Thrombocytopenia Purpura, Systemic Lupus Erythematosus, hemolytic anemia, or fetal maternal incompatibility. In addition, splenomegaly, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, infection or prosthetic heart valves may result in thrombocytopenia. Severe thrombocytopenia may also result from chemotherapy and/or radiation therapy or cancer. Thrombocytopenia may also result from marrow invasion by carcinoma, lymphoma, leukemia or fibrosis.



The IL-3 variants of the present invention, when coadministered or used in sequential treatment with other colony stimulating factors, may be useful in the mobilization of hematopoietic progenitors and stem cells into peripheral blood. Peripheral blood derived progenitors have been shown to be effective in reconstituting patients in the setting of autologous marrow transplantation. Hematopoietic growth factors including G-CSF and GM-CSF have been shown to enhance the number of circulating progenitors and stem cells in the peripheral blood. This has simplified the procedure for peripheral stem cell collection and dramatically decreased the cost of the procedure by decreasing the number of pheresis required. The IL-3 variants, when coadministered or used in sequential treatment with other colony stimulating factors, may be useful in mobilization of stem cells and further enhance the efficacy of peripheral stem cell transplantation.

Another projected clinical use of growth factors has been in the in vitro activation of hematopoietic progenitors and stem cells for gene therapy. In order to have the gene of interest incorporated into the genome of the hematopoietic progenitor or stem cell one needs to stimulate cell division and DNA replication. Hematopoietic stem cells cycle at a very low frequency which means that growth factors may be useful to promote gene transduction and thereby enhance the clinical prospects for gene therapy.

Many drugs may cause bone marrow suppression or hematopoietic deficiencies. Examples of such drugs are AZT, DDI, alkylating agents and anti-metabolites used in chemotherapy, antibiotics such as chloramphenicol, penicillin, gancyclovir, daunomycin and sulfa drugs,

phenothiazones, tranquilizers such as meprobamate, analgesics such as aminopyrine and dipyrone, anticonvulsants such as phenytoin or carbamazepine, antithyroids such as propylthiouracil and methimazole and diuretics. Coadministration or sequential treatment using IL-3 variants of the present invention with other colony stimulating factors may be useful in preventing or treating the bone marrow suppression or hematopoietic deficiencies which often occur in patients treated with these drugs.

Hematopoietic deficiencies may also occur as a result of viral, microbial or parasitic infections and as a result of treatment for renal disease or renal failure, e.g., dialysis. Coadministration or sequential treatment using IL-3 variants of the present invention with other colony stimulating factors may be useful in treating such hematopoietic deficiency.

The treatment of hematopoietic deficiency may include administration of a pharmaceutical composition containing the IL-3 variants with other colony stimulating factors to a patient. Coadministration or sequential treatment using IL-3 variants of the present invention with other colony stimulating factors may also be useful for the activation and amplification of hematopoietic precursor cells by treating these cells in vitro with the coadministration or sequential treatment using IL-3 variants of the present invention with other colony stimulating factors prior to injecting the cells into a patient.

Various immunodeficiencies e.g., in T and/or B lymphocytes, or immune disorders, e.g., rheumatoid arthritis, may also be beneficially affected by treatment with the coadministration or sequential treatment using IL-3 variants of the present invention with other colony stimulating factors molecules of the present invention. Immunodeficiencies may be the result of viral infections e.g. HTLV I, HTLV II, HTLV III,

severe exposure to radiation, cancer therapy or the result of other medical treatment. IL-3 variants of the present invention may also be employed, alone or in combination with other hematopoietins, in the treatment of other blood cell deficiencies, including thrombocytopenia (platelet deficiency), or anemia. Other uses for these novel polypeptides are in the treatment of patients recovering from bone marrow transplants in vivo and ex vivo, and in the development of monoclonal and polyclonal antibodies generated by standard methods for diagnostic or therapeutic use.

Other aspects of the present invention are methods and therapeutic compositions for treating the conditions referred to above. Such compositions comprise a therapeutically effective amount of one or more of the IL-3 variants of the present invention with other colony stimulating factors in a mixture with a pharmaceutically acceptable carrier. This composition can be administered either parenterally, intravenously or subcutaneously. When administered, the therapeutic composition for use in this invention is preferably in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such a parenterally acceptable protein solution, having due regard to pH, isotonicity, stability and the like, is within the skill of the art.

The dosage regimen involved in a method for treating the above-described conditions will be determined by the attending physician considering various factors which modify the action of drugs, e.g. the condition, body weight, sex and diet of the patient, the severity of any infection, time of administration and other clinical factors. Generally, a daily regimen may be in the range of 0.2 - 150  $\mu$ g/kg of IL-3 variant protein per kilogram of body weight. This dosage regimen is referenced to a standard level of biological activity which recognizes that native IL-

3 generally possesses an EC<sub>50</sub> at or about 10 picoMolar to 100 picoMolar in the AML proliferation assay described herein. Therefore, dosages would be adjusted relative to the activity of a given IL-3 variant

5 protein vs. the activity of native (reference) IL-3 and it would not be unreasonable to note that dosage regimens may include doses as low as 0.1 microgram and as high as 1 milligram per kilogram of body weight per day. In addition, there may exist specific

10 circumstances where dosages of IL-3 variant protein would be adjusted higher or lower than the range of 10 - 200 micrograms per kilogram of body weight. These include co-administration with other CSF, cytokine, lymphokine, interleukin, hematopoietic growth factor or

15 IL-3 variant or growth factors; co-administration with chemotherapeutic drugs and/or radiation; the use of glycosylated IL-3 proteins; and various patient-related issues mentioned earlier in this section. As indicated above, the therapeutic method and compositions may also

20 include co-administration with other human factors. A non-exclusive list of other appropriate hematopoietins, CSFs, cytokines, lymphokines, hematopoietic growth factors and interleukins for simultaneous or serial co-administration with the polypeptides of the present

25 invention includes GM-CSF, CSF-1, G-CSF, Meg-CSF (more recently referred to as c-mpl ligand), M-CSF, erythropoietin (EPO), IL-1, IL-4, IL-2, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, LIF, flt3/flk2, human growth hormone, B-cell growth factor,

30 B-cell differentiation factor and eosinophil differentiation factor, stem cell factor (SCF) also known as steel factor or c-kit ligand, or combinations thereof. The dosage recited above would be adjusted to compensate for such additional components in the

35 therapeutic composition. Progress of the treated patient can be monitored by periodic assessment of the hematological profile, e.g., differential cell count

and the like.

The present invention includes the following  
5 compositions:

1. A composition comprising:

A human interleukin-3 mutant polypeptide of the  
Formula:

10 Ala Pro Met Thr Gln Thr Thr Ser Leu Lys Thr Ser Trp Val Asn  
1 5 10 15  
15 Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa  
20 25 30  
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asn Xaa Xaa Xaa Xaa Xaa Xaa  
35 40 45  
20 Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa  
50 55 60  
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa  
65 70 75  
25 Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa  
80 85 90  
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa  
95 100 105  
30 Xaa Phe Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa  
110 115 120  
35 Xaa Xaa Xaa Gln Gln Thr Thr Leu Ser Leu Ala Ile Phe  
125 130

[SEQ ID NO:1]

wherein

Xaa at position 17 is Ser, Lys, Gly, Asp, Met, Gln, or Arg;

5 Xaa at position 18 is Asn, His, Leu, Ile, Phe, Arg, or Gln;

Xaa at position 19 is Met, Phe, Ile, Arg, Gly, Ala, or Cys;

Xaa at position 20 is Ile, Cys, Gln, Glu, Arg, Pro, or

10 Ala;

Xaa at position 21 is Asp, Phe, Lys, Arg, Ala, Gly, Glu, Gln, Asn, Thr, Ser or Val;

Xaa at position 22 is Glu, Trp, Pro, Ser, Ala, His, Asp, Asn, Gln, Leu, Val or Gly;

15 Xaa at position 23 is Ile, Val, Ala, Leu, Gly, Trp, Lys, Phe, Leu, Ser, or Arg;

Xaa at position 24 is Ile, Gly, Val, Arg, Ser, Phe, or Leu;

Xaa at position 25 is Thr, His, Gly, Gln, Arg, Pro, or

20 Ala;

Xaa at position 26 is His, Thr, Phe, Gly, Arg, Ala, or Trp;

Xaa at position 27 is Leu, Gly, Arg, Thr, Ser, or Ala;

Xaa at position 28 is Lys, Arg, Leu, Gln, Gly, Pro, Val or

25 Trp;

Xaa at position 29 is Gln, Asn, Leu, Pro, Arg, or Val;

Xaa at position 30 is Pro, His, Thr, Gly, Asp, Gln, Ser, Leu, or Lys;

Xaa at position 31 is Pro, Asp, Gly, Ala, Arg, Leu, or

30 Gln;

Xaa at position 32 is Leu, Val, Arg, Gln, Asn, Gly, Ala, or Glu;

Xaa at position 33 is Pro, Leu, Gln, Ala, Thr, or Glu;

Xaa at position 34 is Leu, Val, Gly, Ser, Lys, Glu, Gln,

35 Thr, Arg, Ala, Phe, Ile or Met;

Xaa at position 35 is Leu, Ala, Gly, Asn, Pro, Gln, or Val;

## 31

- Xaa at position 36 is Asp, Leu, or Val;  
Xaa at position 37 is Phe, Ser, Pro, Trp, or Ile;  
Xaa at position 38 is Asn, or Ala;  
Xaa at position 40 is Leu, Trp, or Arg;  
5 Xaa at position 41 is Asn, Cys, Arg, Leu, His, Met, or Pro;  
Xaa at position 42 is Gly, Asp, Ser, Cys, Asn, Lys, Thr, Leu, Val, Glu, Phe, Tyr, Ile, Met or Ala;  
Xaa at position 43 is Glu, Asn, Tyr, Leu, Phe, Asp, Ala,  
10 Cys, Gln, Arg, Thr, Gly or Ser;  
Xaa at position 44 is Asp, Ser, Leu, Arg, Lys, Thr, Met, Trp, Glu, Asn, Gln, Ala or Pro;  
Xaa at position 45 is Gln, Pro, Phe, Val, Met, Leu, Thr, Lys, Trp, Asp, Asn, Arg, Ser, Ala, Ile, Glu or His;  
15 Xaa at position 46 is Asp, Phe, Ser, Thr, Cys, Glu, Asn, Gln, Lys, His, Ala, Tyr, Ile, Val or Gly;  
Xaa at position 47 is Ile, Gly, Val, Ser, Arg, Pro, or His;  
Xaa at position 48 is Leu, Ser, Cys, Arg, Ile, His, Phe,  
20 Glu, Lys, Thr, Ala, Met, Val or Asn;  
Xaa at position 49 is Met, Arg, Ala, Gly, Pro, Asn, His, or Asp;  
Xaa at position 50 is Glu, Leu, Thr, Asp, Tyr, Lys, Asn, Ser, Ala, Ile, Val, His, Phe, Met or Gln;  
25 Xaa at position 51 is Asn, Arg, Met, Pro, Ser, Thr, or His;  
Xaa at position 52 is Asn, His, Arg, Leu, Gly, Ser, or Thr;  
Xaa at position 53 is Leu, Thr, Ala, Gly, Glu, Pro, Lys, Ser, or Met;  
30 Xaa at position 54 is Arg, Asp, Ile, Ser, Val, Thr, Gln, Asn, Lys, His, Ala or Leu;  
Xaa at position 55 is Arg, Thr, Val, Ser, Leu, or Gly;  
Xaa at position 56 is Pro, Gly, Cys, Ser, Gln, Glu, Arg,  
35 His, Thr, Ala, Tyr, Phe, Leu, Val or Lys;  
Xaa at position 57 is Asn or Gly;  
Xaa at position 58 is Leu, Ser, Asp, Arg, Gln, Val, or

Cys;

Xaa at position 59 is Glu Tyr, His, Leu, Pro, or Arg;  
Xaa at position 60 is Ala, Ser, Pro, Tyr, Asn, or Thr;  
Xaa at position 61 is Phe, Asn, Glu, Pro, Lys, Arg, or  
5 Ser;  
Xaa at position 62 is Asn His, Val, Arg, Pro, Thr, Asp, or  
Ile;  
Xaa at position 63 is Arg, Tyr, Trp, Lys, Ser, His, Pro,  
or Val;  
10 Xaa at position 64 is Ala, Asn, Pro, Ser, or Lys;  
Xaa at position 65 is Val, Thr, Pro, His, Leu, Phe, or  
Ser;  
Xaa at position 66 is Lys, Ile, Arg, Val, Asn, Glu, or  
Ser;  
15 Xaa at position 67 is Ser, Ala, Phe, Val, Gly, Asn, Ile,  
Pro, or His;  
Xaa at position 68 is Leu, Val, Trp, Ser, Ile, Phe, Thr,  
or His;  
Xaa at position 69 is Gln, Ala, Pro, Thr, Glu, Arg, Trp,  
20 Gly, or Leu;  
Xaa at position 70 is Asn, Leu, Val, Trp, Pro, or Ala;  
Xaa at position 71 is Ala, Met, Leu, Pro, Arg, Glu, Thr,  
Gln, Trp, or Asn;  
Xaa at position 72 is Ser, Glu, Met, Ala, His, Asn, Arg,  
25 or Asp;  
Xaa at position 73 is Ala, Glu, Asp, Leu, Ser, Gly, Thr,  
or Arg;  
Xaa at position 74 is Ile, Met, Thr, Pro, Arg, Gly, Ala;  
Xaa at position 75 is Glu, Lys, Gly, Asp, Pro, Trp, Arg,  
30 Ser, Gln, or Leu;  
Xaa at position 76 is Ser, Val, Ala, Asn, Trp, Glu, Pro,  
Gly, or Asp;  
Xaa at position 77 is Ile, Ser, Arg, Thr, or Leu;  
Xaa at position 78 is Leu, Ala, Ser, Glu, Phe, Gly, or  
35 Arg;  
Xaa at position 79 is Lys, Thr, Asn, Met, Arg, Ile, Gly,  
or Asp;



## 33

- Xaa at position 80 is Asn, Trp, Val, Gly, Thr, Leu, Glu,  
or Arg;
- Xaa at position 81 is Leu, Gln, Gly, Ala, Trp, Arg, Val,  
or Lys;
- 5 Xaa at position 82 is Leu, Gln, Lys, Trp, Arg, Asp, Glu,  
Asn, His, Thr, Ser, Ala, Tyr, Phe, Ile, Met or Val;  
Xaa at position 83 is Pro, Ala, Thr, Trp, Arg, or Met;  
Xaa at position 84 is Cys, Glu, Gly, Arg, Met, or Val;  
Xaa at position 85 is Leu, Asn, Val, or Gln;
- 10 Xaa at position 86 is Pro, Cys, Arg, Ala, or Lys;  
Xaa at position 87 is Leu, Ser, Trp, or Gly;  
Xaa at position 88 is Ala, Lys, Arg, Val, or Trp;  
Xaa at position 89 is Thr, Asp, Cys, Leu, Val, Glu, His,  
Asn, or Ser;
- 15 Xaa at position 90 is Ala, Pro, Ser, Thr, Gly, Asp, Ile,  
or Met;  
Xaa at position 91 is Ala, Pro, Ser, Thr, Phe, Leu, Asp,  
or His;  
Xaa at position 92 is Pro, Phe, Arg, Ser, Lys, His, Ala,
- 20 Gly, Ile or Leu;  
Xaa at position 93 is Thr, Asp, Ser, Asn, Pro, Ala, Leu,  
or Arg;  
Xaa at position 94 is Arg, Ile, Ser, Glu, Leu, Val, Gln,  
Lys, His, Ala, or Pro;
- 25 Xaa at position 95 is His, Gln, Pro, Arg, Val, Leu, Gly,  
Thr, Asn, Lys, Ser, Ala, Trp, Phe, Ile, or Tyr;  
Xaa at position 96 is Pro, Lys, Tyr, Gly, Ile, or Thr;  
Xaa at position 97 is Ile, Val, Lys, Ala, or Asn;  
Xaa at position 98 is His, Ile, Asn, Leu, Asp, Ala, Thr,
- 30 Glu, Gln, Ser, Phe, Met, Val, Lys, Arg, Tyr or Pro;  
Xaa at position 99 is Ile, Leu, Arg, Asp, Val, Pro, Gln,  
Gly, Ser, Phe, or His;  
Xaa at position 100 is Lys, Tyr, Leu, His, Arg, Ile, Ser,  
Gln, or Pro;
- 35 Xaa at position 101 is Asp, Pro, Met, Lys, His, Thr, Val,  
Tyr, Glu, Asn, Ser, Ala, Gly, Ile, Leu, or Gln;  
Xaa at position 102 is Gly, Leu, Glu, Lys, Ser, Tyr, or

- Pro;
- Xaa at position 103 is Asp, or Ser;
- Xaa at position 104 is Trp, Val, Cys, Tyr, Thr, Met, Pro,  
Leu, Gln, Lys, Ala, Phe, or Gly;
- 5 Xaa at position 105 is Asn, Pro, Ala, Phe, Ser, Trp, Gln,  
Tyr, Leu, Lys, Ile, Asp, or His;
- Xaa at position 106 is Glu, Ser, Ala, Lys, Thr, Ile, Gly,  
or Pro;
- Xaa at position 108 is Arg, Lys, Asp, Leu, Thr, Ile, Gln,  
10 His, Ser, Ala or Pro;
- Xaa at position 109 is Arg, Thr, Pro, Glu, Tyr, Leu, Ser,  
or Gly;
- Xaa at position 110 is Lys, Ala, Asn, Thr, Leu, Arg, Gln,  
His, Glu, Ser, Ala, or Trp;
- 15 Xaa at position 111 is Leu, Ile, Arg, Asp, or Met;
- Xaa at position 112 is Thr, Val, Gln, Tyr, Glu, His, Ser,  
or Phe;
- Xaa at position 113 is Phe, Ser, Cys, His, Gly, Trp, Tyr,  
Asp, Lys, Leu, Ile, Val or Asn;
- 20 Xaa at position 114 is Tyr, Cys, His, Ser, Trp, Arg, or  
Leu;
- Xaa at position 115 is Leu, Asn, Val, Pro, Arg, Ala, His,  
Thr, Trp, or Met;
- Xaa at position 116 is Lys, Leu, Pro, Thr, Met, Asp, Val,  
25 Glu, Arg, Trp, Ser, Asn, His, Ala, Tyr, Phe, Gln, or  
Ile;
- Xaa at position 117 is Thr, Ser, Asn, Ile, Trp, Lys, or  
Pro;
- Xaa at position 118 is Leu, Ser, Pro, Ala, Glu, Cys, Asp,  
30 or Tyr;
- Xaa at position 119 is Glu, Ser, Lys, Pro, Leu, Thr, Tyr,  
or Arg;
- Xaa at position 120 is Asn, Ala, Pro, Leu, His, Val, or  
Gln;
- 35 Xaa at position 121 is Ala, Ser, Ile, Asn, Pro, Lys, Asp,  
or Gly;
- Xaa at position 122 is Gln, Ser, Met, Trp, Arg, Phe, Pro,

His, Ile, Tyr, or Cys;  
 Xaa at position 123 is Ala, Met, Glu, His, Ser, Pro, Tyr,  
 or Leu;

- 5 and which can additionally have Met- preceding  
 the amino acid in position 1; and wherein from 1  
 to 14 amino acids can be deleted from the N-  
 terminus and/or from 1 to 15 amino acids can be  
 deleted from the C-terminus; and wherein from 4  
 10 to 44 of the amino acids designated by Xaa are  
 different from the corresponding amino acids of  
 native (1-133) human interleukin-3;

- A colony stimulating factor selected from  
 15 the group consisting of GM-CSF, CSF-1, G-CSF,  
 Meg-CSF (more recently referred to as c-mpl  
 ligand), M-CSF, erythropoietin (EPO), IL-1, IL-4,  
 IL-2, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11,  
 IL-12, IL-13, LIF, flt3/flk2, human growth  
 20 hormone, B-cell growth factor, B-cell  
 differentiation factor, eosinophil  
 differentiation factor and stem cell factor  
 (SCF); and

- At least one non-toxic pharmaceutically  
 25 acceptable carrier.

2 A composition, comprising: A human  
 interleukin-3 mutant polypeptide of the Formula:

- 30 Ala Pro Met Thr Gln Thr Thr Ser Leu Lys Thr Ser Trp Val Asn  
 1 5 10 15

36

	Cys Xaa Xaa Xaa Ile Xaa Glu Xaa Xaa Xaa Xaa Leu Lys Xaa Xaa	
	20	25 30
5	Xaa Xaa Xaa Xaa Xaa Asp Xaa Xaa Asn Leu Asn Xaa Glu Xaa Xaa	
	35	40 45
	Xaa Ile Leu Met Xaa Xaa Asn Leu Xaa Xaa Xaa Asn Leu Glu Xaa	
	50	55 60
10	Phe Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asn Xaa Xaa Xaa Ile Glu	
	65	70 75
	Xaa Xaa Leu Xaa Xaa Leu Xaa Xaa Cys Xaa Pro Xaa Xaa Thr Ala	
	80	85 90
15	Xaa Pro Xaa Arg Xaa Xaa Xaa Xaa Xaa Xaa Gly Asp Xaa Xaa	
	95	100 105
	Xaa Phe Xaa Xaa Lys Leu Xaa Phe Xaa Xaa Xaa Xaa Leu Glu Xaa	
20	110	115 120
	Xaa Xaa Xaa Gln Gln Thr Thr Leu Ser Leu Ala Ile Phe	
	125	130

[SEQ ID NO:2]

25

wherein

Xaa at position 17 is Ser, Gly, Asp, Met, or Gln;

Xaa at position 18 is Asn, His, or Ile;

Xaa at position 19 is Met or Ile;

30 Xaa at position 21 is Asp or Glu;

Xaa at position 23 is Ile, Ala, Leu, or Gly;

Xaa at position 24 is Ile, Val, or Leu;

Xaa at position 25 is Thr, His, Gln, or Ala;

Xaa at position 26 is His or Ala;

35 Xaa at position 29 is Gln, Asn, or Val;

Xaa at position 30 is Pro, Gly, or Gln;

Xaa at position 31 is Pro, Asp, Gly, or Gln;

- Xaa at position 32 is Leu, Arg, Gln, Asn, Gly, Ala, or Glu;
- Xaa at position 33 is Pro or Glu;
- Xaa at position 34 is Leu, Val, Gly, Ser, Lys, Ala, Arg, Gln, Glu, Ile, Phe, Thr or Met;
- 5 Xaa at position 35 is Leu, Ala, Asn, Pro, Gln, or Val;
- Xaa at position 37 is Phe, Ser, Pro, or Trp;
- Xaa at position 38 is Asn or Ala;
- Xaa at position 42 is Gly, Asp, Ser, Cys, Ala, Asn, Ile, Leu, Met, Tyr or Arg;
- 10 Xaa at position 44 is Asp or Glu;
- Xaa at position 45 is Gln, Val, Met, Leu, Thr, Ala, Asn, Glu, Ser or Lys;
- Xaa at position 46 is Asp, Phe, Ser, Thr, Ala, Asn Gln, Glu, His, Ile, Lys, Tyr, Val or Cys;
- 15 Xaa at position 50 is Glu, Ala, Asn, Ser or Asp;
- Xaa at position 51 is Asn, Arg, Met, Pro, Ser, Thr, or His;
- Xaa at position 54 is Arg or Ala;
- 20 Xaa at position 55 is Arg, Thr, Val, Leu, or Gly;
- Xaa at position 56 is Pro, Gly, Ser, Gln, Ala, Arg, Asn, Glu, Leu, Thr, Val or Lys;
- Xaa at position 60 is Ala or Ser;
- Xaa at position 62 is Asn, Pro, Thr, or Ile;
- 25 Xaa at position 63 is Arg or Lys;
- Xaa at position 64 is Ala or Asn;
- Xaa at position 65 is Val or Thr;
- Xaa at position 66 is Lys or Arg;
- Xaa at position 67 is Ser, Phe, or His;
- 30 Xaa at position 68 is Leu, Ile, Phe, or His;
- Xaa at position 69 is Gln, Ala, Pro, Thr, Glu, Arg, or Gly;
- Xaa at position 71 is Ala, Pro, or Arg;
- Xaa at position 72 is Ser, Glu, Arg, or Asp;
- 35 Xaa at position 73 is Ala or Leu;
- Xaa at position 76 is Ser, Val, Ala, Asn, Glu, Pro, or Gly;

- Xaa at position 77 is Ile or Leu;  
Xaa at position 79 is Lys, Thr, Gly, Asn, Met, Arg, Ile,  
Gly, or Asp;  
Xaa at position 80 is Asn, Gly, Glu, or Arg;
- 5 Xaa at position 82 is Leu, Gln, Trp, Arg, Asp, Ala, Asn,  
Glu, His, Ile, Met, Phe, Ser, Thr, Tyr or Val;  
Xaa at position 83 is Pro or Thr;  
Xaa at position 85 is Leu or Val;  
Xaa at position 87 is Leu or Ser;
- 10 Xaa at position 88 is Ala or Trp;  
Xaa at position 91 is Ala or Pro;  
Xaa at position 93 is Thr, Asp, Ser, Pro, Ala, Leu, or  
Arg;  
Xaa at position 95 is His, Pro, Arg, Val, Leu, Gly, Asn,  
Phe, Ser or Thr;
- 15 Xaa at position 96 is Pro or Tyr;  
Xaa at position 97 is Ile or Val;  
Xaa at position 98 is His, Ile, Asn, Leu, Ala, Thr, Leu,  
Arg, Gln, Leu, Lys, Met, Ser, Tyr, Val or Pro;
- 20 Xaa at position 99 is Ile, Leu, or Val;  
Xaa at position 100 is Lys, Arg, Ile, Gln, Pro, or Ser;  
Xaa at position 101 is Asp, Pro, Met, Lys, His, Thr, Pro,  
Asn, Ile, Leu or Tyr;  
Xaa at position 104 is Trp or Leu;
- 25 Xaa at position 105 is Asn, Pro, Ala, Ser, Trp, Gln, Tyr,  
Leu, Lys, Ile, Asp, or His;  
Xaa at position 106 is Glu or Gly;  
Xaa at position 108 is Arg, Ala, or Ser;  
Xaa at position 109 is Arg, Thr, Glu, Leu, or Ser;
- 30 Xaa at position 112 is Thr, Val, or Gln;  
Xaa at position 114 is Tyr or Trp;  
Xaa at position 115 is Leu or Ala;  
Xaa at position 116 is Lys, Thr, Val, Trp, Ser, Ala, His,  
Met, Phe, Tyr or Ile;
- 35 Xaa at position 117 is Thr or Ser;  
Xaa at position 120 is Asn, Pro, Leu, His, Val, or Gln;  
Xaa at position 121 is Ala, Ser, Ile, Asn, Pro, Asp, or

39

Gly;

Xaa at position 122 is Gln, Ser, Met, Trp, Arg, Phe, Pro,  
His, Ile, Tyr, or Cys;

5 Xaa at position 123 is Ala, Met, Glu, His, Ser, Pro, Tyr,  
or Leu.

and which can additionally have Met- preceding  
the amino acid in position 1; and wherein from 1  
to 14 amino acids can be deleted from the N-  
10 terminus and/or from 1 to 15 amino acids can be  
deleted from the C-terminus; and wherein from 4  
to 35 of the amino acids designated by Xaa are  
different from the corresponding amino acids of  
native (1-133)human interleukin-3;

15 A colony stimulating factor selected from  
the group consisting of GM-CSF, CSF-1, G-CSF,  
Meg-CSF (more recently referred to as c-mpl  
ligand), M-CSF, erythropoietin (EPO), IL-1, IL-4,  
IL-2, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11,  
20 IL-12, IL-13, LIF, flt3/flk2, human growth  
hormone, B-cell growth factor, B-cell  
differentiation factor, eosinophil  
differentiation factor and stem cell factor  
(SCF); and

25 At least one non-toxic pharmaceutically  
acceptable carrier.

3. A composition of 2, wherein  
said human interleukin-3 mutant polypeptide is of  
30 the Formula:

	Ala	Pro	Met	Thr	Gln	Thr	Thr	Ser	Leu	Lys	Thr	Ser	Trp	Val	Asn
	1				5					10				15	
35	Cys	Xaa	Xaa	Met	Ile	Asp	Glu	Xaa	Ile	Xaa	Xaa	Leu	Lys	Xaa	Xaa
					20					25				30	

40

	Pro Xaa	Pro Xaa	Xaa Asp	Phe Xaa	Asn Leu	Asn Xaa	Glu Asp	Xaa
			35			40		45
5	Xaa Ile	Leu Met	Xaa Xaa	Asn Leu	Arg Xaa	Xaa Asn	Leu Glu	Ala
			50			55		60
	Phe Xaa	Arg Xaa	Xaa Lys	Xaa Xaa	Xaa Asn	Ala Ser	Ala Ile	Glu
			65			70		75
10	Xaa Xaa	Leu Xaa	Xaa Leu	Xaa Pro	Cys Leu	Pro Xaa	Xaa Thr	Ala
			80			85		90
	Xaa Pro	Xaa Arg	Xaa Pro	Ile Xaa	Xaa Xaa	Xaa Gly	Asp Trp	Xaa
			95			100		105
15	Glu Phe	Xaa Xaa	Lys Leu	Xaa Phe	Tyr Leu	Xaa Xaa	Leu Glu	Xaa
			110			115		120
	Xaa Xaa	Xaa Gln	Gln Thr	Thr Leu	Ser Leu	Ala Ile	Phe	
20			125			130		

[SEQ ID NO:3]

wherein

- 25 Xaa at position 17 is Ser, Gly, Asp, or Gln;  
 Xaa at position 18 is Asn, His, or Ile;  
 Xaa at position 23 is Ile, Ala, Leu, or Gly;  
 Xaa at position 25 is Thr, His, or Gln;  
 Xaa at position 26 is His or Ala;  
 Xaa at position 29 is Gln or Asn;
- 30 Xaa at position 30 is Pro or Gly;  
 Xaa at position 32 is Leu, Arg, Asn, or Ala;  
 Xaa at position 34 is Leu, Val, Ser, Ala, Arg, Gln, Glu,  
 Ile, Phe, Thr, or Met;
- 35 Xaa at position 35 is Leu, Ala, Asn, or Pro;  
 Xaa at position 38 is Asn or Ala;  
 Xaa at position 42 is Gly, Asp, Ser, Ala, Asn, Ile, Leu,  
 Met, Tyr or Arg;



## 41

- Xaa at position 45 is Gln, Val, Met, Leu, Ala, Asn, Glu,  
or Lys;
- Xaa at position 46 is Asp, Phe, Ser, Gln, Glu, His, Val  
or Thr;
- 5 Xaa at position 50 is Glu Asn, Ser or Asp;  
Xaa at position 51 is Asn, Arg, Pro, Thr, or His;  
Xaa at position 55 is Arg, Leu, or Gly;  
Xaa at position 56 is Pro, Gly, Ser, Ala, Asn, Val, Leu or  
Gln;
- 10 Xaa at position 62 is Asn, Pro, or Thr;  
Xaa at position 64 is Ala or Asn;  
Xaa at position 65 is Val or Thr;  
Xaa at position 67 is Ser or Phe;  
Xaa at position 68 is Leu or Phe;
- 15 Xaa at position 69 is Gln, Ala, Glu, or Arg;  
Xaa at position 76 is Ser, Val, Asn, Pro, or Gly;  
Xaa at position 77 is Ile or Leu;  
Xaa at position 79 is Lys, Gly, Asn, Met, Arg, Ile, or  
Gly;
- 20 Xaa at position 80 is Asn, Gly, Glu, or Arg;  
Xaa at position 82 is Leu, Gln, Trp, Arg, Asp, Asn, Glu,  
His, Met, Phe, Ser, Thr, Tyr or Val;  
Xaa at position 87 is Leu or Ser;  
Xaa at position 88 is Ala or Trp;
- 25 Xaa at position 91 is Ala or Pro;  
Xaa at position 93 is Thr, Asp, or Ala;  
Xaa at position 95 is His, Pro, Arg, Val, Gly, Asn, Ser or  
Thr;
- Xaa at position 98 is His, Ile, Asn, Ala, Thr, Gln, Glu,  
Lys, Met, Ser, Tyr, Val or Leu;
- 30 Xaa at position 99 is Ile or Leu;  
Xaa at position 100 is Lys or Arg;  
Xaa at position 101 is Asp, Pro, Met, Lys, Thr, His, Pro,  
Asn, Ile, Leu or Tyr;
- 35 Xaa at position 105 is Asn, Pro, Ser, Ile or Asp;  
Xaa at position 108 is Arg, Ala, or Ser;  
Xaa at position 109 is Arg, Thr, Glu, Leu, or Ser;

42

Xaa at position 112 is Thr or Gln;

Xaa at position 116 is Lys, Val, Trp, Ala, His, Phe, Tyr  
or Ile;

Xaa at position 117 is Thr or Ser;

5 Xaa at position 120 is Asn, Pro, Leu, His, Val, or Gln;

Xaa at position 121 is Ala, Ser, Ile, Pro, or Asp;

Xaa at position 122 is Gln, Met, Trp, Phe, Pro, His, Ile,  
or Tyr;

Xaa at position 123 is Ala, Met, Glu, Ser, or Leu;

10

and which can additionally have Met- preceding  
the amino acid in position 1; and wherein from 1  
to 14 amino acids can be deleted from the N-  
terminus and/or from 1 to 15 amino acids can be  
15 deleted from the C-terminus; and wherein from 4  
to 44 of the amino acids designated by Xaa are  
different from the corresponding amino acids of  
native (1-133)human interleukin-3.

20

4. A composition of 3, wherein said  
human interleukin-3 mutant polypeptide is of the  
Formula:

25

Xaa at position 42 is Gly, Asp, Ser, Ile, Leu, Met, Tyr,  
or Ala;

Xaa at position 45 is Gln, Val, Met or Asn;

Xaa at position 46 is Asp, Ser, Gln, His or Val;

Xaa at position 50 is Glu or Asp;

Xaa at position 51 is Asn, Pro or Thr;

30

Xaa at position 62 is Asn or Pro;

Xaa at position 76 is Ser, or Pro;

Xaa at position 82 is Leu, Trp, Asp, Asn Glu, His, Phe,  
Ser or Tyr;

Xaa at position 95 is His, Arg, Thr, Asn or Ser;

35

Xaa at position 98 is His, Ile, Leu, Ala, Gln, Lys, Met,  
Ser, Tyr or Val;

Xaa at position 100 is Lys or Arg;

43

Xaa at position 101 is Asp, Pro, His, Asn, Ile or Leu;  
 Xaa at position 105 is Asn, or Pro;  
 Xaa at position 108 is Arg, Ala, or Ser;  
 Xaa at position 116 is Lys, Val, Trp, Ala, His, Phe, or  
 5 Tyr;  
 Xaa at position 121 is Ala, or Ile;  
 Xaa at position 122 is Gln, or Ile; and  
 Xaa at position 123 is Ala, Met or Glu.

10 5. A composition, comprising:  
 A human interleukin-3 mutant  
 polypeptide of the Formula:

15	Asn Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa	
	1 5 10 15	
	Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa	
	20 25 30	
20	Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa	
	35 40 45	
	Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa	
	50 55 60	
25	Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa	
	65 70 75	
	Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa	
30	80 85 90	
	Xaa Xaa Phe Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa	
	95 100 105	
35	Xaa Xaa Xaa Xaa Gln Gln [SEQ ID NO:4]	
	110	

wherein

- Xaa at position 3 is Ser, Lys, Gly, Asp, Met, Gln, or Arg;  
Xaa at position 4 is Asn, His, Leu, Ile, Phe, Arg, or Gln;  
Xaa at position 5 is Met, Phe, Ile, Arg, Gly, Ala, or Cys;  
5 Xaa at position 6 is Ile, Cys, Gln, Glu, Arg, Pro, or Ala;  
Xaa at position 7 is Asp, Phe, Lys, Arg, Ala, Gly, Glu,  
Gln, Asn, Thr, Ser or Val;  
Xaa at position 8 is Glu, Trp, Pro, Ser, Ala, His, Asp,  
Asn, Gln, Leu, Val, or Gly;  
10 Xaa at position 9 is Ile, Val, Ala, Leu, Gly, Trp, Lys,  
Phe, Leu, Ser, or Arg;  
Xaa at position 10 is Ile, Gly, Val, Arg, Ser, Phe, or  
Leu;  
Xaa at position 11 is Thr, His, Gly, Gln, Arg, Pro, or  
15 Ala;  
Xaa at position 12 is His, Thr, Phe, Gly, Arg, Ala, or  
Trp;  
Xaa at position 13 is Leu, Gly, Arg, Thr, Ser, or Ala;  
Xaa at position 14 is Lys, Arg, Leu, Gln, Gly, Pro, Val or  
20 Trp;  
Xaa at position 15 is Gln, Asn, Leu, Pro, Arg, or Val;  
Xaa at position 16 is Pro, His, Thr, Gly, Asp, Gln, Ser,  
Leu, or Lys;  
Xaa at position 17 is Pro, Asp, Gly, Ala, Arg, Leu, or  
25 Gln;  
Xaa at position 18 is Leu, Val, Arg, Gln, Asn, Gly, Ala,  
or Glu;  
Xaa at position 19 is Pro, Leu, Gln, Ala, Thr, or Glu;  
Xaa at position 20 is Leu, Val, Gly, Ser, Lys, Glu, Gln,  
30 Thr, Arg, Ala, Phe, Ile or Met;  
Xaa at position 21 is Leu, Ala, Gly, Asn, Pro, Gln, or  
Val;  
Xaa at position 22 is Asp, Leu, or Val;  
Xaa at position 23 is Phe, Ser, Pro, Trp, or Ile;  
35 Xaa at position 24 is Asn, or Ala;  
Xaa at position 26 is Leu, Trp, or Arg;  
Xaa at position 27 is Asn, Cys, Arg, Leu, His, Met, Pro;

- Xaa at position 28 is Gly, Asp, Ser, Cys, Ala, Lys, Asn,  
Thr, Leu, Val, Glu, Phe, Tyr, Ile or Met;
- Xaa at position 29 is Glu, Asn, Tyr, Leu, Phe, Asp, Ala,  
Cys, Gln, Arg, Thr, Gly or Ser;
- 5 Xaa at position 30 is Asp, Ser, Leu, Arg, Lys, Thr, Met,  
Trp, Glu, Asn, Gln, Ala or Pro;
- Xaa at position 31 is Gln, Pro, Phe, Val, Met, Leu, Thr,  
Lys, Asp, Asn, Arg, Ser, Ala, Ile, Glu, His or Trp;
- Xaa at position 32 is Asp, Phe, Ser, Thr, Cys, Glu, Asn,  
10 Gln, Lys, His, Ala, Tyr, Ile, Val or Gly;
- Xaa at position 33 is Ile, Gly, Val, Ser, Arg, Pro, or  
His;
- Xaa at position 34 is Leu, Ser, Cys, Arg, Ile, His, Phe,  
Glu, Lys, Thr, Ala, Met, Val or Asn;
- 15 Xaa at position 35 is Met, Arg, Ala, Gly, Pro, Asn, His,  
or Asp;
- Xaa at position 36 is Glu, Leu, Thr, Asp, Tyr, Lys, Asn,  
Ser, Ala, Ile, Val, His, Phe, Met or Gln;
- Xaa at position 37 is Asn, Arg, Met, Pro, Ser, Thr, or  
20 His;
- Xaa at position 38 is Asn, His, Arg, Leu, Gly, Ser, or  
Thr;
- Xaa at position 39 is Leu, Thr, Ala, Gly, Glu, Pro, Lys,  
Ser, Met, or;
- 25 Xaa at position 40 is Arg, Asp, Ile, Ser, Val, Thr, Gln,  
Asn, Lys, His, Ala or Leu;
- Xaa at position 41 is Arg, Thr, Val, Ser, Leu, or Gly;
- Xaa at position 42 is Pro, Gly, Cys, Ser, Gln, Glu, Arg,  
His, Thr, Ala, Tyr, Phe, Leu, Val or Lys;
- 30 Xaa at position 43 is Asn or Gly;
- Xaa at position 44 is Leu, Ser, Asp, Arg, Gln, Val, or  
Cys;
- Xaa at position 45 is Glu Tyr, His, Leu, Pro, or Arg;
- Xaa at position 46 is Ala, Ser, Pro, Tyr, Asn, or Thr;
- 35 Xaa at position 47 is Phe, Asn, Glu, Pro, Lys, Arg, or  
Ser;
- Xaa at position 48 is Asn, His, Val, Arg, Pro, Thr, Asp,

- or Ile;
- Xaa at position 49 is Arg, Tyr, Trp, Lys, Ser, His, Pro,  
or Val;
- Xaa at position 50 is Ala, Asn, Pro, Ser, or Lys;
- 5 Xaa at position 51 is Val, Thr, Pro, His, Leu, Phe, or  
Ser;
- Xaa at position 52 is Lys, Ile, Arg, Val, Asn, Glu, or  
Ser;
- Xaa at position 53 is Ser, Ala, Phe, Val, Gly, Asn, Ile,  
10 Pro, or His;
- Xaa at position 54 is Leu, Val, Trp, Ser, Ile, Phe, Thr,  
or His;
- Xaa at position 55 is Gln, Ala, Pro, Thr, Glu, Arg, Trp,  
Gly, or Leu;
- 15 Xaa at position 56 is Asn, Leu, Val, Trp, Pro, or Ala;
- Xaa at position 57 is Ala, Met, Leu, Pro, Arg, Glu, Thr,  
Gln, Trp, or Asn;
- Xaa at position 58 is Ser, Glu, Met, Ala, His, Asn, Arg,  
or Asp;
- 20 Xaa at position 59 is Ala, Glu, Asp, Leu, Ser, Gly, Thr,  
or Arg;
- Xaa at position 60 is Ile, Met, Thr, Pro, Arg, Gly, Ala;
- Xaa at position 61 is Glu, Lys, Gly, Asp, Pro, Trp, Arg,  
Ser, Gln, or Leu;
- 25 Xaa at position 62 is Ser, Val, Ala, Asn, Trp, Glu, Pro,  
Gly, or Asp;
- Xaa at position 63 is Ile, Ser, Arg, Thr, or Leu;
- Xaa at position 64 is Leu, Ala, Ser, Glu, Phe, Gly, or  
Arg;
- 30 Xaa at position 65 is Lys, Thr, Gly, Asn, Met, Arg, Ile,  
or Asp;
- Xaa at position 66 is Asn, Trp, Val, Gly, Thr, Leu, Glu,  
or Arg;
- Xaa at position 67 is Leu, Gln, Gly, Ala, Trp, Arg, Val,  
35 or Lys;
- Xaa at position 68 is Leu, Gln, Lys, Trp, Arg, Asp, Glu,  
Asn, His, Thr, Ser, Ala, Tyr, Phe, Ile, Met or Val;

- Xaa at position 69 is Pro, Ala, Thr, Trp, Arg, or Met;  
Xaa at position 70 is Cys, Glu, Gly, Arg, Met, or Val;  
Xaa at position 71 is Leu, Asn, Val, or Gln;  
Xaa at position 72 is Pro, Cys, Arg, Ala, or Lys;  
5 Xaa at position 73 is Leu, Ser, Trp, or Gly;  
Xaa at position 74 is Ala, Lys, Arg, Val, or Trp;  
Xaa at position 75 is Thr, Asp, Cys, Leu, Val, Glu, His,  
Asn, or Ser;  
Xaa at position 76 is Ala, Pro, Ser, Thr, Gly, Asp, Ile,  
10 or Met;  
Xaa at position 77 is Ala, Pro, Ser, Thr, Phe, Leu, Asp,  
or His;  
Xaa at position 78 is Pro, Phe, Arg, Ser, Lys, His, Ala,  
Gly, Ile or Leu;  
15 Xaa at position 79 is Thr, Asp, Ser, Asn, Pro, Ala, Leu,  
or Arg;  
Xaa at position 80 is Arg, Ile, Ser, Glu, Leu, Val, Gln,  
Lys, His, Ala or Pro;  
Xaa at position 81 is His, Gln, Pro, Arg, Val, Leu, Gly,  
20 Thr, Asn, Lys, Ser, Ala, Trp, Phe, Ile or Tyr;  
Xaa at position 82 is Pro, Lys, Tyr, Gly, Ile, or Thr;  
Xaa at position 83 is Ile, Val, Lys, Ala, or Asn;  
Xaa at position 84 is His, Ile, Asn, Leu, Asp, Ala, Thr,  
Glu, Gln, Ser, Phe, Met, Val, Lys, Arg, Tyr or Pro;  
25 Xaa at position 85 is Ile, Leu, Arg, Asp, Val, Pro, Gln,  
Gly, Ser, Phe, or His;  
Xaa at position 86 is Lys, Tyr, Leu, His, Arg, Ile, Ser,  
Gln, Pro;  
Xaa at position 87 is Asp, Pro, Met, Lys, His, Thr, Val,  
30 Tyr, Glu, Asn, Ser, Ala, Gly, Ile, Leu or Gln;  
Xaa at position 88 is Gly, Leu, Glu, Lys, Ser, Tyr, or  
Pro;  
Xaa at position 89 is Asp, or Ser;  
Xaa at position 90 is Trp, Val, Cys, Tyr, Thr, Met, Pro,  
35 Leu, Gln, Lys, Ala, Phe, or Gly;  
Xaa at position 91 is Asn, Pro, Ala, Phe, Ser, Trp, Gln,  
Tyr, Leu, Lys, Ile, Asp, or His;

## 48

- Xaa at position 92 is Glu, Ser, Ala, Lys, Thr, Ile, Gly,  
or Pro;
- Xaa at position 94 is Arg, Lys, Asp, Leu, Thr, Ile, Gln,  
His, Ser, Ala, or Pro;
- 5 Xaa at position 95 is Arg, Thr, Pro, Glu, Tyr, Leu, Ser,  
or Gly;
- Xaa at position 96 is Lys, Asn, Thr, Leu, Gln, Arg,  
His, Glu, Ser, Ala or Trp;
- Xaa at position 97 is Leu, Ile, Arg, Asp, or Met;
- 10 Xaa at position 98 is Thr, Val, Gln, Tyr, Glu, His, Ser,  
or Phe;
- Xaa at position 99 is Phe, Ser, Cys, His, Gly, Trp, Tyr,  
Asp, Lys, Leu, Ile, Val or Asn;
- Xaa at position 100 is Tyr, Cys, His, Ser, Trp, Arg, or  
15 Leu;
- Xaa at position 101 is Leu, Asn, Val, Pro, Arg, Ala, His,  
Thr, Trp, or Met;
- Xaa at position 102 is Lys, Leu, Pro, Thr, Met, Asp, Val,  
Glu, Arg, Trp, Ser, Asn, His, Ala, Tyr, Phe, Gln, or  
20 Ile;
- Xaa at position 103 is Thr, Ser, Asn, Ile, Trp, Lys, or  
Pro;
- Xaa at position 104 is Leu, Ser, Pro, Ala, Glu, Cys, Asp,  
or Tyr;
- 25 Xaa at position 105 is Glu, Ser, Lys, Pro, Leu, Thr, Tyr,  
or Arg;
- Xaa at position 106 is Asn, Ala, Pro, Leu, His, Val, or  
Gln;
- Xaa at position 107 is Ala, Ser, Ile, Asn, Pro, Lys, Asp,  
30 or Gly;
- Xaa at position 108 is Gln, Ser, Met, Trp, Arg, Phe, Pro,  
His, Ile, Tyr, or Cys;
- Xaa at position 109 is Ala, Met, Glu, His, Ser, Pro, Tyr,  
or Leu;
- 35 and which can additionally have Met- or Met-Ala-  
preceding the amino acid in position 1; and



5        A colony stimulating factor selected from  
the group consisting of GM-CSF, CSF-1, G-CSF,  
Meg-CSF (more recently referred to as c-mpl  
ligand), M-CSF, erythropoietin (EPO), IL-1, IL-4,  
IL-2, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11,  
10 IL-12, IL-13, LIF, flt3/flk2, human growth  
hormone, B-cell growth factor, B-cell  
differentiation factor, eosinophil  
differentiation factor and stem cell factor  
(SCF): and

6. A composition of 5, wherein  
said human interleukin-3 mutant polypeptide is of  
the Formula:

25    Xaa Xaa Xaa Xaa Xaa Xaa Asp Xaa Xaa Asn Leu Asn Xaa Glu Xaa  
                        20                        25                        30

30  
Xaa Phe Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asn Xaa Xaa Xaa Ile  
50 55 60

Ala Xaa Pro Xaa Arg Xaa Xaa Xaa Xaa Xaa Xaa Xaa Gly Asp Xaa

50

80

85

90

Xaa Xaa Phe Xaa Xaa Lys Leu Xaa Phe Xaa Xaa Xaa Xaa Leu Glu  
 95 100 105

5

Xaa Xaa Xaa Xaa Gln Gln [SEQ ID NO:5]  
 110

wherein

- 10 Xaa at position 3 is Ser, Gly, Asp, Met, or Gln;  
 Xaa at position 4 is Asn, His, or Ile;  
 Xaa at position 5 is Met or Ile;  
 Xaa at position 7 is Asp or Glu;  
 Xaa at position 9 is Ile, Ala, Leu, or Gly;
- 15 Xaa at position 10 is Ile, Val, or Leu;  
 Xaa at position 11 is Thr, His, Gln, or Ala;  
 Xaa at position 12 is His or Ala;  
 Xaa at position 15 is Gln, Asn, or Val;  
 Xaa at position 16 is Pro, Gly, or Gln;
- 20 Xaa at position 17 is Pro, Asp, Gly, or Gln;  
 Xaa at position 18 is Leu, Arg, Gln, Asn, Gly, Ala, or  
 Glu;  
 Xaa at position 19 is Pro or Glu;  
 Xaa at position 20 is Leu, Val, Gly, Ser, Lys, Ala, Arg,
- 25 Gln, Glu, Ile, Phe, Thr or Met;  
 Xaa at position 21 is Leu, Ala, Asn, Pro, Gln, or Val;  
 Xaa at position 23 is Phe, Ser, Pro, or Trp;  
 Xaa at position 24 is Asn or Ala;  
 Xaa at position 28 is Gly, Asp, Ser, Cys, Ala, Asn, Ile,
- 30 Leu, Met Tyr or Arg;  
 Xaa at position 30 is Asp or Glu;  
 Xaa at position 31 is Gln, Val, Met, Leu, Thr, Ala, Asn,  
 Glu, Ser or Lys;  
 Xaa at position 32 is Asp, Phe, Ser, Thr, Ala, Asn, Gln,
- 35 Glu, His, Ile, Lys, Tyr, Val or Cys;  
 Xaa at position 36 is Glu, Ala, Asn, Ser or Asp;  
 Xaa at position 37 is Asn, Arg, Met, Pro, Ser, Thr, or

## 51

His;

Xaa at position 40 is Arg or Ala;

Xaa at position 41 is Arg, Thr, Val, Leu, or Gly;

Xaa at position 42 is Pro, Gly, Ser, Gln, Ala, Arg, Asn,

5       Glu, Leu, Thr, Val or Lys;

Xaa at position 46 is Ala or Ser;

Xaa at position 48 is Asn, Pro, Thr, or Ile;

Xaa at position 49 is Arg or Lys;

Xaa at position 50 is Ala or Asn;

10       Xaa at position 51 is Val or Thr;

Xaa at position 52 is Lys or Arg;

Xaa at position 53 is Ser, Phe, or His;

Xaa at position 54 is Leu, Ile, Phe, or His;

Xaa at position 55 is Gln, Ala, Pro, Thr, Glu, Arg, or

15       Gly;

Xaa at position 57 is Ala, Pro, or Arg;

Xaa at position 58 is Ser, Glu, Arg, or Asp;

Xaa at position 59 is Ala or Leu;

Xaa at position 62 is Ser, Val, Ala, Asn, Glu, Pro, or

20       Gly;

Xaa at position 63 is Ile or Leu;

Xaa at position 65 is Lys, Thr, Gly, Asn, Met, Arg, Ile,

      Gly, or Asp;

Xaa at position 66 is Asn, Gly, Glu, or Arg;

25       Xaa at position 68 is Leu, Gln, Trp, Arg, Asp, Ala, Asn,

      Glu, His, Ile, Met, Phe, Ser, Thr, Tyr or Val;

Xaa at position 69 is Pro or Thr;

Xaa at position 71 is Leu or Val;

Xaa at position 73 is Leu or Ser;

30       Xaa at position 74 is Ala or Trp;

Xaa at position 77 is Ala or Pro;

Xaa at position 79 is Thr, Asp, Ser, Pro, Ala, Leu, or

      Arg;

Xaa at position 81 is His, Pro, Arg, Val, Leu, Gly, Asn,

35       Phe, Ser or Thr;

Xaa at position 82 is Pro or Tyr;

Xaa at position 83 is Ile or Val;

- Xaa at position 84 is His, Ile, Asn, Leu, Ala, Thr, Leu,  
Arg, Gln, Leu, Lys, Met, Ser, Tyr, Val or Pro;  
Xaa at position 85 is Ile, Leu, or Val;  
Xaa at position 86 is Lys, Arg, Ile, Gln, Pro, or Ser;  
5 Xaa at position 87 is Asp, Pro, Met, Lys, His, Thr, Asn,  
Ile, Leu or Tyr;  
Xaa at position 90 is Trp or Leu;  
Xaa at position 91 is Asn, Pro, Ala, Ser, Trp, Gln, Tyr,  
Leu, Lys, Ile, Asp, or His;  
10 Xaa at position 92 is Glu, or Gly;  
Xaa at position 94 is Arg, Ala, or Ser;  
Xaa at position 95 is Arg, Thr, Glu, Leu, or Ser;  
Xaa at position 98 is Thr, Val, or Gln;  
Xaa at position 100 is Tyr or Trp;  
15 Xaa at position 101 is Leu or Ala;  
Xaa at position 102 is Lys, Thr, Val, Trp, Ser, Ala, His,  
Met, Phe, Tyr or Ile;  
Xaa at position 103 is Thr or Ser;  
Xaa at position 106 is Asn, Pro, Leu, His, Val, or Gln;  
20 Xaa at position 107 is Ala, Ser, Ile, Asn, Pro, Asp, or  
Gly;  
Xaa at position 108 is Gln, Ser, Met, Trp, Arg, Phe, Pro,  
His, Ile, Tyr, or Cys;  
Xaa at position 109 is Ala, Met, Glu, His, Ser, Pro, Tyr,  
25 or Leu;

- which can additionally have Met- or Met-Ala-  
preceding the amino acid in position 1; and  
wherein from 4 to 35 of the amino acids  
30 designated by Xaa are different from the  
corresponding amino acids of native human  
interleukin-3.

7. A composition of 6, wherein  
35 said human interleukin-3 mutant polypeptide is of  
the Formula:

Xaa Xaa Xaa Xaa Gln Gln [SEQ ID NO:6]

- Xaa at position 28 is Gly, Asp, Ser, Ala, Asn, Ile, Leu,  
Met, Tyr or Arg;
- Xaa at position 31 is Gln, Val, Met, Leu, Ala, Asn, Glu or  
Lys;
- 5 Xaa at position 32 is Asp, Phe, Ser, Ala, Gln, Glu, His,  
Val or Thr;
- Xaa at position 36 is Glu, Asn, Ser or Asp;
- Xaa at position 37 is Asn, Arg, Pro, Thr, or His;
- Xaa at position 41 is Arg, Leu, or Gly;
- 10 Xaa at position 42 is Pro, Gly, Ser, Ala, Asn, Val, Leu or  
Gln;
- Xaa at position 48 is Asn, Pro, or Thr;
- Xaa at position 50 is Ala or Asn;
- Xaa at position 51 is Val or Thr;
- 15 Xaa at position 53 is Ser or Phe;
- Xaa at position 54 is Leu or Phe;
- Xaa at position 55 is Gln, Ala, Glu, or Arg;
- Xaa at position 62 is Ser, Val, Asn, Pro, or Gly;
- Xaa at position 63 is Ile or Leu;
- 20 Xaa at position 65 is Lys, Asn, Met, Arg, Ile, or Gly;
- Xaa at position 66 is Asn, Gly, Glu, or Arg;
- Xaa at position 68 is Leu, Gln, Trp, Arg, Asp, Asn, Glu,  
His, Met, Phe, Ser, Thr, Tyr or Val;
- Xaa at position 73 is Leu or Ser;
- 25 Xaa at position 74 is Ala or Trp;
- Xaa at position 77 is Ala or Pro;
- Xaa at position 79 is Thr, Asp, or Ala;
- Xaa at position 81 is His, Pro, Arg, Val, Gly, Asn, Ser or  
Thr;
- 30 Xaa at position 84 is His, Ile, Asn, Ala, Thr, Arg, Gln,  
Glu, Lys, Met, Ser, Tyr, Val or Leu;
- Xaa at position 85 is Ile or Leu;
- Xaa at position 86 is Lys or Arg;
- Xaa at position 87 is Asp, Pro, Met, Lys, His, Pro, Asn,
- 35 Ile, Leu or Tyr;
- Xaa at position 91 is Asn, Pro, Ser, Ile or Asp;
- Xaa at position 94 is Arg, Ala, or Ser;

55

- Xaa at position 95 is Arg, Thr, Glu, Leu, or Ser;  
Xaa at position 98 is Thr or Gln;  
Xaa at position 102 is Lys, Val, Trp, or Ile;  
Xaa at position 103 is Thr, Ala, His, Phe, Tyr or Ser;  
5 Xaa at position 106 is Asn, Pro, Leu, His, Val, or Gln;  
Xaa at position 107 is Ala, Ser, Ile, Pro, or Asp;  
Xaa at position 108 is Gln, Met, Trp, Phe, Pro, His, Ile,  
or Tyr;  
Xaa at position 109 is Ala, Met, Glu, Ser, or Leu;  
10  
and which can additionally have Met- or Met-Ala-  
preceding the amino acid in position 1; and  
wherein from 4 to 26 of the amino acids  
designated by Xaa are different from the  
15 corresponding amino acids of native (1-133)human  
interleukin-3.

8. The composition of 7, wherein  
said human interleukin-3 mutant polypeptide is of  
20 the Formula:

- Xaa at position 17 is Ser, Lys, Asp, Met, Gln, or Arg;  
Xaa at position 18 is Asn, His, Leu, Ile, Phe, Arg, or \ Gln;  
25 Xaa at position 19 is Met, Arg, Gly, Ala, or Cys;  
Xaa at position 20 is Ile, Cys, Gln, Glu, Arg, Pro, or Ala;  
Xaa at position 21 is Asp, Phe, Lys, Arg, Ala, Gly, or Val;  
30 Xaa at position 22 is Glu, Trp, Pro, Ser, Ala, His, or Gly;  
Xaa at position 23 is Ile, Ala, Gly, Trp, Lys, Leu, Ser, or Arg;  
Xaa at position 24 is Ile, Gly, Arg, or Ser;  
35 Xaa at position 25 is Thr, His, Gly, Gln, Arg, Pro, or Ala;  
Xaa at position 26 is His, Thr, Phe, Gly, Ala, or Trp;

## 56

- Xaa at position 27 is Leu, Gly, Arg, Thr, Ser, or Ala;  
Xaa at position 28 is Lys, Leu, Gln, Gly, Pro, Val or Trp;  
Xaa at position 29 is Gln, Asn, Pro, Arg, or Val;  
Xaa at position 30 is Pro, His, Thr, Gly, Asp, Gln, Ser,  
5 Leu, or Lys;  
Xaa at position 31 is Pro, Asp, Gly, Arg, Leu, or Gln;  
Xaa at position 32 is Leu, Arg, Gln, Asn, Gly, Ala, or  
Glu;  
Xaa at position 33 is Pro, Leu, Gln, Thr, or Glu;  
10 Xaa at position 34 is Leu, Gly, Ser, or Lys;  
Xaa at position 35 is Leu, Ala, Gly, Asn, Pro, or Gln;  
Xaa at position 36 is Asp, Leu, or Val;  
Xaa at position 37 is Phe, Ser, or Pro;  
Xaa at position 38 is Asn, or Ala;  
15 Xaa at position 40 is Leu, Trp, or Arg;  
Xaa at position 41 is Asn, Cys, Arg, Leu, His, Met, Pro;  
Xaa at position 42 is Gly, Asp, Ser, Cys, or Ala;  
Xaa at position 42 is Glu, Asn, Tyr, Leu, Phe, Asp, Ala,  
Cys, or Ser;  
20 Xaa at position 44 is Asp, Ser, Leu, Arg, Lys, Thr, Met,  
Trp, or Pro;  
Xaa at position 45 is Gln, Pro, Phe, Val, Met, Leu, Thr,  
Lys, or Trp;  
Xaa at position 46 is Asp, Phe, Ser, Thr, Cys, or Gly;  
25 Xaa at position 47 is Ile, Gly, Ser, Arg, Pro, or His;  
Xaa at position 48 is Leu, Ser, Cys, Arg, His, Phe, or  
Asn;  
Xaa at position 49 is Met, Arg, Ala, Gly, Pro, Asn, His,  
or Asp;  
30 Xaa at position 50 is Glu, Leu, Thr, Asp, or Tyr;  
Xaa at position 51 is Asn, Arg, Met, Pro, Ser, Thr, or  
His;  
Xaa at position 52 is Asn, His, Arg, Leu, Gly, Ser, or  
Thr;  
35 Xaa at position 53 is Leu, Thr, Ala, Gly, Glu, Pro, Lys,  
Ser, or;  
Xaa at position 54 is Arg, Asp, Ile, Ser, Val, Thr, Gln,



- or Leu;
- Xaa at position 55 is Arg, Thr, Val, Ser, Leu, or Gly;  
Xaa at position 56 is Pro, Gly, Cys, Ser, Gln, or Lys;  
Xaa at position 57 is Asn or Gly;
- 5 Xaa at position 58 is Leu, Ser, Asp, Arg, Gln, Val, or Cys;  
Xaa at position 59 is Glu Tyr, His, Leu, Pro, or Arg;  
Xaa at position 60 is Ala, Ser, Tyr, Asn, or Thr;  
Xaa at position 61 is Phe, Asn, Glu, Pro, Lys, Arg, or
- 10 Ser;  
Xaa at position 62 is Asn His, Val, Arg, Pro, Thr, or Ile;  
Xaa at position 63 is Arg, Tyr, Trp, Ser, Pro, or Val;  
Xaa at position 64 is Ala, Asn, Ser, or Lys;  
Xaa at position 65 is Val, Thr, Pro, His, Leu, Phe, or
- 15 Ser;  
Xaa at position 66 is Lys, Ile, Val, Asn, Glu, or Ser;  
Xaa at position 67 is Ser, Ala, Phe, Val, Gly, Asn, Ile, Pro, or His;  
Xaa at position 68 is Leu, Val, Trp, Ser, Thr, or His;
- 20 Xaa at position 69 is Gln, Ala, Pro, Thr, Arg, Trp, Gly, or Leu;  
Xaa at position 70 is Asn, Leu, Val, Trp, Pro, or Ala;  
Xaa at position 71 is Ala, Met, Leu, Arg, Glu, Thr, Gln, Trp, or Asn;
- 25 Xaa at position 72 is Ser, Glu, Met, Ala, His, Asn, Arg, or Asp;  
Xaa at position 73 is Ala, Glu, Asp, Leu, Ser, Gly, Thr, or Arg;  
Xaa at position 74 is Ile, Thr, Pro, Arg, Gly, Ala;
- 30 Xaa at position 75 is Glu, Lys, Gly, Asp, Pro, Trp, Arg, Ser, or Leu;  
Xaa at position 76 is Ser, Val, Ala, Asn, Trp, Glu, Pro, Gly, or Asp;  
Xaa at position 77 is Ile, Ser, Arg, or Thr;
- 35 Xaa at position 78 is Leu, Ala, Ser, Glu, Gly, or Arg;  
Xaa at position 79 is Lys, Thr, Gly, Asn, Met, Ile, or Asp;

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- Xaa at position 80 is Asn, Trp, Val, Gly, Thr, Leu, or Arg;
- Xaa at position 81 is Leu, Gln, Gly, Ala, Trp, Arg, or Lys;
- 5 Xaa at position 82 is Leu, Gln, Lys, Trp, Arg, or Asp;  
Xaa at position 83 is Pro, Thr, Trp, Arg, or Met;  
Xaa at position 84 is Cys, Glu, Gly, Arg, Met, or Val;  
Xaa at position 85 is Leu, Asn, or Gln;  
Xaa at position 86 is Pro, Cys, Arg, Ala, or Lys;
- 10 Xaa at position 87 is Leu, Ser, Trp, or Gly;  
Xaa at position 88 is Ala, Lys, Arg, Val, or Trp;  
Xaa at position 89 is Thr, Asp, Cys, Leu, Val, Glu, His, or Asn;
- Xaa at position 90 is Ala, Ser, Asp, Ile, or Met;
- 15 Xaa at position 91 is Ala, Ser, Thr, Phe, Leu, Asp, or His;
- Xaa at position 92 is Pro, Phe, Arg, Ser, Lys, His, or Leu;
- Xaa at position 93 is Thr, Asp, Ser, Asn, Pro, Ala, Leu, or Arg;
- 20 Xaa at position 94 is Arg, Ile, Ser, Glu, Leu, Val, or Pro;
- Xaa at position 95 is His, Gln, Pro, Val, Leu, Thr or Tyr;
- Xaa at position 96 is Pro, Lys, Tyr, Gly, Ile, or Thr;
- 25 Xaa at position 97 is Ile, Lys, Ala, or Asn;
- Xaa at position 98 is His, Ile, Asn, Leu, Asp, Ala, Thr, or Pro;
- Xaa at position 99 is Ile, Arg, Asp, Pro, Gln, Gly, Phe, or His;
- 30 Xaa at position 100 is Lys, Tyr, Leu, His, Ile, Ser, Gln, or Pro;
- Xaa at position 101 is Asp, Pro, Met, Lys, His, Thr, Val, Tyr, or Gln;
- Xaa at position 102 is Gly, Leu, Glu, Lys, Ser, Tyr, or Pro;
- 35 Xaa at position 103 is Asp, or Ser;
- Xaa at position 104 is Trp, Val, Cys, Tyr, Thr, Met, Pro,

59

Leu, Gln, Lys, Ala, Phe, or Gly;

Xaa at position 105 is Asn, Pro, Ala, Phe, Ser, Trp, Gln,

Tyr, Leu, Lys, Ile, or His;

Xaa at position 106 is Glu, Ser, Ala, Lys, Thr, Ile, Gly,

5 or Pro;

Xaa at position 108 is Arg, Asp, Leu, Thr, Ile, or Pro;

60

Xaa at position 109 is Arg, Thr, Pro, Glu, Tyr, Leu, Ser,  
or Gly.

9.A composition of 8, wherein said  
5 human interleukin-3 mutant polypeptide is of the  
Formula:

	1		5		10
	(Met) <sub>m</sub> -Ala	Pro	Met	Thr	Gln Thr Thr Ser Leu Lys Thr
10		15		20	
	Ser Trp Val	Asn Cys Ser	Xaa Xaa Xaa	Asp Glu Ile Ile	
25		30		35	
	Xaa His Leu	Lys Xaa Pro	Pro Xaa Pro	Xaa Leu Asp Xaa	
		40		45	50
15	Xaa Asn Leu	Asn Xaa Glu	Asp Xaa Asp	Ile Leu Xaa Glu	
		55		60	
	Xaa Asn Leu	Arg Xaa Xaa	Asn Leu Xaa	Xaa Phe Xaa Xaa	
		65		70	75
	Ala Xaa Lys	Xaa Leu Xaa	Asn Ala Ser	Xaa Ile Glu Xaa	
20		80		85	
	Ile Leu Xaa	Asn Leu Xaa	Pro Cys Xaa	Pro Xaa Xaa Thr	
		90		95	100
	Ala Xaa Pro	Xaa Arg Xaa	Pro Ile Xaa	Ile Xaa Xaa Gly	
		105		110	115
25	Asp Trp Xaa	Glu Phe Arg	Xaa Lys Leu	Xaa Phe Tyr Leu	
		120		125	
	Xaa Xaa Leu	Glu Xaa Ala	Gln Xaa Gln	Gln Thr Thr Leu	
		130			
30	Ser Leu Ala	Ile Phe	[SEQ ID NO:7]		

wherein m is 0 or 1; Xaa at position 18 is Asn or  
Ile; Xaa at position 19 is Met, Ala or Ile; Xaa  
at position 20 is Ile, Pro or Ile; Xaa at  
position 23 is Ile, Ala or Leu; Xaa at position  
35 25 is Thr or His; Xaa at position 29 is Gln, Arg,  
Val or Ile; Xaa at position 32 is Leu, Ala, Asn  
or Arg; Xaa at position 34 is Leu or Ser; Xaa at

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position 37 is Phe, Pro, or Ser; Xaa at position 38 is Asn or Ala; Xaa at position 42 is Gly, Ala, Ser, Asp or Asn; Xaa at position 45 is Gln, Val, or Met; Xaa at position 46 is Asp or Ser; Xaa at position 49 is Met, Ile, Leu or Asp; Xaa at position 50 is Glu or Asp; Xaa at position 51 is Asn Arg or Ser; Xaa at position 55 is Arg, Leu, or Thr; Xaa at position 56 is Pro or Ser; Xaa at position 59 is Glu or Leu; Xaa at position 60 is Ala or Ser; Xaa at position 62 is Asn, Val or Pro; Xaa at position 63 is Arg or His; Xaa at position 65 is Val or Ser; Xaa at position 67 is Ser, Asn, His or Gln; Xaa at position 69 is Gln or Glu; Xaa at position 73 is Ala or Gly; Xaa at position 76 is Ser, Ala or Pro; Xaa at position 79 is Lys, Arg or Ser; Xaa at position 82 is Leu, Glu, Val or Trp; Xaa at position 85 is Leu or Val; Xaa at position 87 is Leu, Ser, Tyr; Xaa at position 88 is Ala or Trp; Xaa at position 91 is Ala or Pro; Xaa at position 93 is Pro or Ser; Xaa at position 95 is His or Thr; Xaa at position 98 is His, Ile, or Thr; Xaa at position 100 is Lys or Arg; Xaa at position 101 is Asp, Ala or Met; Xaa at position 105 is Asn or Glu; Xaa at position 109 is Arg, Glu or Leu; Xaa at position 112 is Thr or Gln; Xaa at position 116 is Lys, Val, Trp or Ser; Xaa at position 117 is Thr or Ser; Xaa at position 120 is Asn, Gln, or His; Xaa at position 123 is Ala or Glu; with the proviso that from four to forty-four of the amino acids designated by Xaa are different from the corresponding amino acids of native human interleukin-3.

10. The composition of 9, wherein said human interleukin-3 mutant polypeptide is of the Formula:

```

              1              5              10
(Metm-Alan)p-Asn Cys Ser Xaa Xaa Xaa Asp Glu Xaa
Ile
5              15              20
Xaa His Leu Lys Xaa Pro Pro Xaa Pro Xaa Leu Asp Xaa
    25              30              35
Xaa Asn Leu Asn Xaa Glu Asp Xaa Xaa Ile Leu Xaa Glu
    40              45
10 Xaa Asn Leu Arg Xaa Xaa Asn Leu Xaa Phe Xaa Xaa
    50              55              60
Ala Xaa Lys Xaa Leu Xaa Asn Ala Ser Xaa Ile Glu Xaa
    65              70              75
Ile Leu Xaa Asn Xaa Xaa Pro Cys Xaa Pro Xaa Ala Thr
15              80              85
Ala Xaa Pro Xaa Arg Xaa Pro Ile Xaa Ile Xaa Xaa Gly
    90              95              100
Asp Trp Xaa Glu Phe Arg Xaa Lys Leu Xaa Phe Tyr Leu
    105              110
20 Xaa Xaa Leu Glu Xaa Ala Gln Xaa Gln Gln
[SEQ ID NO:8]

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wherein m is 0 or 1; n is 0 or 1; p is 0 or 1;  
 Xaa at position 4 is Asn or Ile; Xaa at position  
 25 5 is Met, Ala or Ile; Xaa at position 6 is Ile,  
 Pro or Leu; Xaa at position 9 is Ile, Ala or Leu;  
 Xaa at position 11 is Thr or His; Xaa at position  
 15 is Gln, Arg, Val or Ile; Xaa at position 18 is  
 Leu, Ala, Asn or Arg; Xaa at position 20 is Leu  
 30 or Ser; Xaa at position 23 is Phe, Pro, or Ser;  
 Xaa at position 24 is Asn or Ala; Xaa at position  
 28 is Gly, Ala, Ser, Asp or Asn; Xaa at position  
 31 is Gln, Val, or Met; Xaa at position 32 is Asp  
 or Ser; Xaa at position 35 is Met, Ile or Asp;  
 35 Xaa at position 36 is Glu or Asp; Xaa at position  
 37 is Asn, Arg or Ser; Xaa at position 41 is Arg,  
 Leu, or Thr; Xaa at position 42 is Pro or Ser;

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Xaa at position 45 is Glu or Leu; Xaa at position 46 is Ala or Ser; Xaa at position 48 is Asn, Val or Pro; Xaa at position 49 is Arg or His; Xaa at position 51 is Val or Ser; Xaa at position 53 is Ser, Asn, His or Gln; Xaa at position 55 is Gln or Glu; Xaa at position 59 is Ala or Gly; Xaa at position 62 is Ser, Ala or Pro; Xaa at position 65 is Lys, Arg or Ser; Xaa at position 67 is Leu, Glu, or Val; Xaa at position 68 is Leu, Glu, Val or Trp; Xaa at position 71 is Leu or Val; Xaa at position 73 is Leu, Ser or Tyr; Xaa at position 74 is Ala or Trp; Xaa at position 77 is Ala or Pro; Xaa at position 79 is Pro or Ser; Xaa at position 81 is His or Thr; Xaa at position 84 is His, Ile, or Thr; Xaa at position 86 is Lys or Arg; Xaa at position 87 is Asp, Ala or Met; Xaa at position 91 is Asn or Glu; Xaa at position 95 is Arg, Glu, Leu; Xaa at position 98 Thr or Gln; Xaa at position 102 is Lys, Val, Trp or Ser; Xaa at position 103 is Thr or Ser; Xaa at position 106 is Asn, Gln, or His; Xaa at position 109 is Ala or Glu; with the proviso that from four to forty-four of the amino acids designated by Xaa are different from the corresponding amino acids of native (15-125)human interleukin-3.

11. The composition of 10, wherein said human interleukin-3 mutant polypeptide is of the Formula:

30

Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His  
His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro  
Asn Asn Leu Asn Ala Glu Asp Val Asp Ile Leu Met  
Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe  
Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala  
Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu  
Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile

35

64

His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg  
 Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala  
 Gln Ala Gln Gln [SEQ ID NO:9];

5 Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His  
 His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp Pro  
 Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu Met  
 Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe  
 Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala  
 10 Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu  
 Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile  
 His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg  
 Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala  
 Gln Ala Gln Gln [SEQ ID NO:10];

15 Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His  
 His Leu Lys Val Pro Pro Ala Pro Leu Leu Asp Ser  
 Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu Met  
 Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe  
 20 Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala  
 Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu  
 Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile  
 His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg  
 Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala  
 25 Gln Ala Gln Gln [SEQ ID NO:11];

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr  
 His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe  
 Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met  
 30 Glu Arg Asn Leu Arg Leu Pro Asn Leu Leu Ala Phe  
 Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Ala  
 Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu  
 Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile  
 His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg  
 35 Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala  
 Gln Ala Gln Gln [SEQ ID NO:12];



65

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr  
 His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe  
 Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met  
 Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe  
 5 Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Ala  
 Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu  
 Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile  
 His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg  
 Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala  
 10 Gln Ala Gln Gln [SEQ ID NO:13];

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr  
 His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe  
 Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met  
 15 Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe  
 Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Ala  
 Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu  
 Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile  
 His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg  
 20 Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala  
 Gln Ala Gln Gln [SEQ ID NO:14];

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr  
 His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe  
 25 Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met  
 Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe  
 Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly  
 Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu  
 Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile  
 30 Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Arg  
 Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala  
 Gln Ala Gln Gln [SEQ ID NO:15];

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr  
 35 His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe  
 Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met  
 Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe

66

Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly  
Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys Leu  
Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile  
Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Arg  
5 Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala  
Gln Ala Gln Gln [SEQ ID NO:16];

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr  
His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe  
10 Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met  
Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe  
Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala  
Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu  
Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile  
15 His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Glu  
Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala  
Gln Glu Gln Gln [SEQ ID NO:17];

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr  
20 His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe  
Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met  
Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe  
Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala  
Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu  
25 Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile  
His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Glu  
Lys Leu Thr Phe Tyr Leu Val Ser Leu Glu His Ala  
Gln Glu Gln Gln [SEQ ID NO:18];

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr  
His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe  
Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met  
Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe  
Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly  
35 Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu  
Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile  
Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu

Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala  
Gln Glu Gln Gln [SEQ ID NO:19];

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr  
5 His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe  
Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met  
Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe  
Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly  
Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys Leu  
10 Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile  
Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu  
Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala  
Gln Glu Gln Gln [SEQ ID NO:20];

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr  
His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe  
Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met  
Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe  
Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly  
20 Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys Leu  
Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile  
Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu  
Lys Leu Thr Phe Tyr Leu Val Ser Leu Glu His Ala  
Gln Glu Gln Gln [SEQ ID NO:21];

25 Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His  
His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro  
Asn Asn Leu Asn Ala Glu Asp Val Asp Ile Leu Met  
Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe  
30 Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Ala  
Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu  
Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile  
His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg  
Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala  
35 Gln Ala Gln Gln [SEQ ID NO:22];

Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His

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His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp Pro  
Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu Met  
Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe  
Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Ala  
5 Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu  
Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile  
His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg  
Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala  
Gln Ala Gln Gln [SEQ ID NO:23];

10 Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His  
His Leu Lys Val Pro Pro Ala Pro Leu Leu Asp Ser  
Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu Met  
Glu Arg Asn Leu Arg Leu Pro Asn Leu Leu Ala Phe  
15 Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Ala  
Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu  
Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile  
His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg  
Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala  
20 Gln Ala Gln Gln [SEQ ID NO:24];

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile  
Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp  
Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu  
25 Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala  
Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser  
Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys  
Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro  
Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg  
30 Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln  
Ala Gln Glu Gln Gln [SEQ ID NO:25];

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile  
Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp  
35 Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu  
Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala  
Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser

Gly Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys  
 Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro  
 Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg  
 Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln  
 5 Ala Gln Glu Gln Gln [SEQ ID NO:26];

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile  
 Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp  
 Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu  
 10 Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala  
 Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser  
 Gly Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys  
 Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro  
 Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg  
 15 Glu Lys Leu Thr Phe Tyr Leu Val Ser Leu Glu His  
 Ala Gln Glu Gln Gln [SEQ ID NO:27];

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile  
 His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp  
 20 Pro Asn Asn Leu Asn Ala Glu Asp Val Asp Ile Leu  
 Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser  
 Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser  
 Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys  
 Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro  
 25 Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg  
 Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn  
 Ala Gln Ala Gln Gln [SEQ ID NO:28];

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile  
 30 His His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp  
 Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu  
 Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala  
 Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser  
 Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys  
 35 Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro  
 Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg  
 Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn

Ala Gln Ala Gln Gln [SEQ ID NO:29];

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile  
His His Leu Lys Val Pro Pro Ala Pro Leu Leu Asp  
5 Ser Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu  
Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Leu Ala  
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser  
Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys  
Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro  
10 Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg  
Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn  
Ala Gln Ala Gln Gln [SEQ ID NO:30];

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile  
15 His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp  
Pro Asn Asn Leu Asn Ala Glu Asp Val Asp Ile Leu  
Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser  
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser  
Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys  
20 Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro  
Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg  
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln  
Ala Gln Glu Gln Gln [SEQ ID NO:31];

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile  
His His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp  
Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu  
Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala  
Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser  
30 Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys  
Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro  
Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg  
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln  
Ala Gln Glu Gln Gln [SEQ ID NO:32];  
35

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile  
His His Leu Lys Val Pro Pro Ala Pro Leu Leu Asp

Ser Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu  
 Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Leu Ala  
 Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser  
 Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys  
 5 Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro  
 Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg  
 Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln  
 Ala Gln Glu Gln Gln [SEQ ID NO:33];

10 Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile  
 His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp  
 Pro Asn Asn Leu Asn Ala Glu Asp Val Asp Ile Leu  
 Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser  
 Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser  
 15 Gly Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys  
 Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro  
 Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg  
 Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln  
 Ala Gln Glu Gln Gln [SEQ ID NO:34];

20 Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile  
 His His Leu Lys Val Pro Pro Ala Pro Leu Leu Asp  
 Ser Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu  
 Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Leu Ala  
 25 Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser  
 Gly Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys  
 Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro  
 Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg  
 Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln  
 30 Ala Gln Glu Gln Gln [SEQ ID NO:35];

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile  
 His His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp  
 Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu  
 35 Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala  
 Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser  
 Gly Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys

Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro  
 Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg  
 Glu Lys Leu Thr Phe Tyr Leu Val Ser Leu Glu His  
 Ala Gln Glu Gln Gln [SEQ ID NO:36];

5

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile  
 His His Leu Lys Val Pro Pro Ala Pro Leu Leu Asp  
 Ser Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu  
 Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Leu Ala

10

Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser  
 Gly Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys  
 Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro  
 Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg  
 Glu Lys Leu Thr Phe Tyr Leu Val Ser Leu Glu His

15

Ala Gln Glu Gln Gln [SEQ ID NO:37];

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile  
 His His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp  
 Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu

20

Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala  
 Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser  
 Gly Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys  
 Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro  
 Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg

25

Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln  
 Ala Gln Glu Gln Gln [SEQ ID NO:38];

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile  
 His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp

30

Pro Asn Asn Leu Asn Ala Glu Asp Val Asp Ile Leu  
 Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser  
 Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser  
 Gly Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys  
 Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro

35

Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg  
 Glu Lys Leu Thr Phe Tyr Leu Val Ser Leu Glu His  
 Ala Gln Glu Gln Gln [SEQ ID NO:39].



Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile  
His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp  
5 Pro Asn Asn Leu Asn Ala Glu Asp Val Asp Ile Leu  
Met Asp Arg Asn Leu Arg Leu Ser Asn Leu Glu Ser  
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser  
Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys  
Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro  
10 Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg  
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln  
Ala Gln Glu Gln Gln [SEQ ID NO:40]

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ala Ile  
15 His His Leu Lys Arg Pro Pro Ala Pro Ser Leu Asp  
Pro Asn Asn Leu Asn Asp Glu Asp Met Ser Ile Leu  
Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser  
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser  
Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys  
20 Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro  
Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg  
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln  
Ala Gln Glu Gln Gln [SEQ ID NO:41]

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile  
His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp  
Pro Asn Asn Leu Asn Asp Glu Asp Met Ser Ile Leu  
Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser  
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser  
30 Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys  
Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro  
Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg  
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln  
Ala Gln Glu Gln Gln [SEQ ID NO:42]

35

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile  
His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp  
Pro Asn Asn Leu Asn Ala Glu Asp Val Asp Ile Leu

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Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser  
 Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser  
 Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys  
 Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro  
 5 Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg  
 Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln  
 Ala Gln Glu Gln Gln [SEQ ID NO:43]

10 Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile  
 His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp  
 Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu  
 Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser  
 Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser  
 15 Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys  
 Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro  
 Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg  
 Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln  
 Ala Gln Glu Gln Gln [SEQ ID NO:44]

20

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile  
 His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp  
 Pro Asn Asn Leu Asn Asp Glu Asp Met Ser Ile Leu  
 25 Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser  
 Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser  
 Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys  
 Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro  
 Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg  
 30 Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln  
 Ala Gln Glu Gln Gln [SEQ ID NO:45]

35 Met Ala Tyr Pro Glu Thr Asp Tyr Lys Asp Asp Asp  
 Asp Lys Asn Cys Ser Ile Met Ile Asp Glu Ile Ile  
 His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp  
 Pro Asn Asn Leu Asn Ala Glu Asp Val Asp Ile Leu  
 Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser

75

Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser  
 Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys  
 Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro  
 Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg  
 5 Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln  
 Ala Gln Glu Gln Gln [SEQ ID NO:46]

Met Ala Tyr Pro Glu Thr Asp Tyr Lys Asp Asp Asp  
 10 Asp Lys Asn Cys Ser Ile Met Ile Asp Glu Ile Ile  
 His His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp  
 Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu  
 Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala  
 Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser  
 15 Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys  
 Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro  
 Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg  
 Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln  
 Ala Gln Glu Gln Gln [SEQ ID NO:47] and

20 Met Ala Asn Cys Ser Ile Met Ile Asp Glu Leu Ile  
 His His Leu Lys Ile Pro Pro Asn Pro Ser Leu Asp  
 Ser Ala Asn Leu Asn Ser Glu Asp Val Ser Ile Leu  
 Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala  
 25 Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser  
 Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys  
 Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro  
 Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg  
 Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln  
 30 Ala Gln Glu Gln Gln [SEQ ID NO:48].

12. The composition of claim 11,  
 wherein said human interleukin-3 mutant  
 polypeptide is of the Formula:

35 Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile  
 His His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp  
 Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu

Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala  
 Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser  
 Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys  
 Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro  
 5 Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg  
 Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln  
 Ala Gln Glu Gln Gln [SEQ ID NO:32].

Also included in the present invention  
 10 is a method of increasing multi-lineage  
 hematopoietic cell production in a mammal in need  
 thereof comprising administering a  
 pharmaceutically effective amount of a human  
 interleukin-3 mutant polypeptide as disclosed  
 15 above with CSF preferably G-CSF or GM-CSF more  
 preferably G-CSF simultaneously as a composition  
 or one after the other.

Materials and methods for IL-3 variant Expression in  
 20 E. coli

Unless noted otherwise, all specialty chemicals  
 were obtained from Sigma Co., (St. Louis, MO).  
 Restriction endonucleases, T4 poly-nucleotides kinase,  
E. coli DNA polymerase I large fragment (Klenow) and T4  
 25 DNA ligase were obtained from New England Biolabs  
 (Beverly, Massachusetts).

Escherichia coli strains

Strain JM101: delta (pro lac), supE, thi,  
 30 F'(traD36, rpoAB, lacI-Q, lacZdeltaM15) (Messing,  
 1979). This strain can be obtained from the American  
 Type Culture Collection (ATCC), 12301 Parklawn Drive,  
 Rockville, Maryland 20852, accession number 33876.  
 MON105 (W3110 rpoH358) is a derivative of W3110  
 35 (Bachmann, 1972) and has been assigned ATCC accession  
 number 55204. Strain GM48: dam-3, dcm-6, gal, ara,  
 lac, thr, leu, tonA, tsx (Marinus, 1973) was used to

make plasmid DNA that is not methylated at the sequence GATC.

#### Genes and plasmids

The gene used for hIL-3 production in *E. coli* was  
5 obtained from British Biotechnology Incorporated,  
Cambridge, England, catalogue number BBG14. This gene  
is carried on a pUC based plasmid designated pP0518.  
Many other human CSF genes can be obtained from R&D  
Systems, Inc. (Minn, MN) including IL-1 alpha, IL-1  
10 beta, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, G-CSF, GM-CSF  
and LIF.

The plasmids used for production of hIL-3 in  
*E. coli* contain genetic elements whose use has been  
described (Olins et al., 1988; Olins and Rangwala,  
15 1990). The replicon used is that of pBR327  
(Covarrubias, et al., 1981) which is maintained at a  
copy number of about 100 in the cell (Soberon et al.,  
1980). A gene encoding the beta-lactamase protein is  
present on the plasmids. This protein confers  
20 ampicillin resistance on the cell. This resistance  
serves as a selectable phenotype for the presence of  
the plasmid in the cell.

For cytoplasmic expression vectors the  
transcription promoter is derived from the recA gene of  
25 *E. coli* (Sancar et al., 1980). This promoter,  
designated preCA, includes the RNA polymerase binding  
site and the lexA repressor binding site (the  
operator). This segment of DNA provides high level  
transcription that is regulated even when the recA  
30 promoter is on a plasmid with the pBR327 origin of  
replication (Olins et al., 1988) incorporated herein  
by reference.

The ribosome binding site used is that from  
35 gene 10 of phage T7 (Olins et al., 1988). This is  
encoded in a 100 base pair (bp) fragment placed  
adjacent to preCA. In the plasmids used herein, the

recognition sequence for the enzyme *NcoI* (CCATGG) follows the *g10-L*. It is at this *NcoI* site that the *hIL-3* genes were joined to the plasmid. It is expected that the nucleotide sequence at this junction will be recognized in mRNA as a functional start site for translation (Olins et al., 1988). The *hIL-3* genes used were engineered to have a *HindIII* recognition site (AAGCTT) downstream from the coding sequence of the gene. At this *HindIII* site is a 514 base pair *RsaI* fragment containing the origin of replication of the single stranded phage *f1* (Dente et al., 1983; Olins, et al., 1990) both incorporated herein by reference. A plasmid containing these elements is *pMON2341*. Another plasmid containing these elements is *pMON5847* which has been deposited at the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852 under the accession number ATCC 68912.

In secretion expression plasmids the transcription promoter is derived from the *ara B*, *A*, and *D* genes of *E.coli* (Greenfield et al., 1978). This promoter is designated *pAraBAD* and is contained on a 323 base pair *SacII*, *BglII* restriction fragment. The *LamB* secretion leader (Wong et al., 1988, Clement et al., 1981) is fused to the N-terminus of the *hIL-3* gene at the recognition sequence for the enzyme *NcoI* (5'CCATGG3'). The *hIL-3* genes used were engineered to have a *HindIII* recognition site (5'AAGCTT3') following the coding sequence of the gene.

#### **Recombinant DNA methods**

##### Synthetic gene assembly

The *hIL-3* variant genes and other CSF genes can be constructed by the assembly of synthetic oligonucleotides. Synthetic oligonucleotides were designed so that they would anneal in complementary

pairs, with protruding single stranded ends, and when the pairs were properly assembled would result in a DNA sequence that encoded a portion of the desired gene. Amino acid substitutions in the hIL-3 gene were made by  
5 designing the oligonucleotides to encode the desired substitutions. The complementary oligonucleotides were annealed at concentration of 1 picomole per microliter in ligation buffer plus 50mM NaCl. The samples were heated in a 100 ml beaker of boiling water and  
10 permitted to cool slowly to room temperature. One picomole of each of the annealed pairs of oligonucleotides were ligated with approximately 0.2 picomoles of plasmid DNA, digested with the appropriate restriction enzymes, in ligation buffer (25 mM Tris pH  
15 8.0, 10 mM MgCl<sub>2</sub>, 10 mM dithiothreitol, 1 mM ATP, 2mM spermidine) with T4 DNA ligase obtained from New England Biolabs (Beverly, Massachusetts) in a total volume of 20  $\mu$ l at room temperature overnight.

## 20 Polymerase Chain Reaction

Polymerase Chain Reaction (hereafter referred to as PCR) techniques (Saiki, 1985) used the reagent kit and thermal cycler from Perkin-Elmer Cetus (Norwalk, CT.). PCR is based on a thermostable DNA polymerase  
25 from Thermus aquaticus. The PCR technique is a DNA amplification method that mimics the natural DNA replication process in that the number of DNA molecules doubles after each cycle, in a way similar to in vivo replication. The DNA polymerase mediated extension is  
30 in a 5' to 3' direction. The term "primer" as used herein refers to an oligonucleotide sequence that provides an end to which the DNA polymerase can add nucleotides that were complementary to a nucleotide sequence. The latter nucleotide sequence is referred to  
35 as the "template", to which the primers were annealed. The amplified PCR product is defined as the region comprised between the 5' ends of the extension primers.

Since the primers have defined sequences, the product will have discrete ends, corresponding to the primer sequences. The primer extension reaction is carried out using 20 picomoles (pmoles) of each of the

5 oligonucleotides and 1 picogram of template plasmid DNA for 35 cycles (1 cycle is defined as 94 degrees C for one minute, 50 degrees C for two minutes and 72 degrees for three minutes.). The reaction mixture was extracted with an equal volume of phenol/chloroform (50% phenol

10 and 50% chloroform, volume to volume) to remove proteins. The aqueous phase, containing the amplified DNA, and solvent phase were separated by centrifugation for 5 minutes in a microcentrifuge (Model 5414 Eppendorf Inc, Fremont CA.). To precipitate the

15 amplified DNA the aqueous phase was removed and transferred to a fresh tube to which was added 1/10 volume of 3M NaOAc (pH 5.2) and 2.5 volumes of ethanol (100% stored at minus 20 degrees C). The solution was mixed and placed on dry ice for 20 minutes. The DNA was

20 pelleted by centrifugation for 10 minutes in a microcentrifuge and the solution was removed from the pellet. The DNA pellet was washed with 70% ethanol, ethanol removed and dried in a speedvac concentrator (Savant, Farmingdale, New York). The pellet was

25 resuspended in 25 microliters of TE (20mM Tris-HCl pH 7.9, 1mM EDTA). Alternatively the DNA was precipitated by adding equal volume of 4M NH<sub>4</sub>OAc and one volume of isopropanol [Trecro et al., (1988)]. The solution was mixed and incubated at room temperature for 10 minutes

30 and centrifuged. These conditions selectively precipitate DNA fragments larger than ~ 20 bases and were used to remove oligonucleotide primers. One quarter of the reaction was digested with restriction enzymes [Higuchi, (1989)] and on completion heated to 70

35 degrees C to inactivate the enzymes.

Recovery of recombinant plasmids from ligation mixes



*E. coli* JM101 cells were made competent to take up DNA. Typically, 20 to 100 ml of cells were grown in LB medium to a density of approximately 150 Klett units and then collected by centrifugation. The cells were resuspended in one half culture volume of 50 mM CaCl<sub>2</sub> and held at 4°C for one hour. The cells were again collected by centrifugation and resuspended in one tenth culture volume of 50 mM CaCl<sub>2</sub>. DNA was added to a 150 microliter volume of these cells, and the samples were held at 4°C for 30 minutes. The samples were shifted to 42°C for one minute, one milliliter of LB was added, and the samples were shaken at 37°C for one hour. Cells from these samples were spread on plates containing ampicillin to select for transformants. The plates were incubated overnight at 37°C. Single colonies were picked, grown in LB supplemented with ampicillin overnight at 37°C with shaking. From these cultures DNA was isolated for restriction analysis.

## 20 Culture medium

LB medium (Maniatis et al., 1982) was used for growth of cells for DNA isolation. M9 minimal medium supplemented with 1.0% casamino acids, acid hydrolyzed casein, Difco (Detroit, Michigan) was used for cultures in which recombinant IL-3 variant was produced. The ingredients in the M9 medium were as follows: 3g/liter KH<sub>2</sub>PO<sub>4</sub>, 6g/l Na<sub>2</sub>HPO<sub>4</sub>, 0.5 g/l NaCl, 1 g/l NH<sub>4</sub>Cl, 1.2 mM MgSO<sub>4</sub>, 0.025 mM CaCl<sub>2</sub>, 0.2% glucose (0.2% glycerol with the AraBAD promoter), 1% casamino acids, 0.1 ml/l trace minerals (per liter 108 g FeCl<sub>3</sub>·6H<sub>2</sub>O, 4.0 g ZnSO<sub>4</sub>·7H<sub>2</sub>O, 7.0 CoCl<sub>2</sub>·2H<sub>2</sub>O, 7.0 g Na<sub>2</sub>MoO<sub>4</sub>·2H<sub>2</sub>O, 8.0 g CuSO<sub>4</sub>·5H<sub>2</sub>O, 2.0 g H<sub>3</sub>BO<sub>3</sub>, 5.0 g MnSO<sub>4</sub>·H<sub>2</sub>O, 100 ml concentrated HCl). Bacto agar was used for solid media and ampicillin was added to both liquid and solid LB media at 200 micrograms per milliliter.

## Production of IL-3 variants in *E. coli* with vectors

employing the recA promoter

*E. coli* strains harboring the plasmids of interest were grown at 37°C in M9 plus casamino acids medium with shaking in a Gyrotory water bath Model G76 from New Brunswick Scientific (Edison, New Jersey). Growth was monitored with a Klett Summerson meter (green 54 filter), Klett Mfg. Co. (New York, New York). At a Klett value of approximately 150, an aliquot of the culture (usually one milliliter) was removed for protein analysis. To the remaining culture, nalidixic acid (10mg/ml) in 0.1 N NaOH was added to a final concentration of 50 µg/ml. The cultures were shaken at 37°C for three to four hours after addition of nalidixic acid. A high degree of aeration was maintained throughout the bacterial growth in order to achieve maximal production of the desired gene product. The cells were examined under a light microscope for the presence of refractile bodies (RBs). One milliliter aliquots of the culture were removed for analysis of protein content.

Extraction, Refolding and Purification of IL-3 Variant Proteins Expressed as Refractile bodies in *E. coli*

Extraction of refractile bodies (RB's):

For each gram of RB's (and typically one gram is obtained from a 300 ml *E. coli* culture), 5 ml of a solution containing 6M guanidine hydrochloride (GnHCl), 50 mM 2-N-cyclohexylaminoethanesulfonic acid (CHES) pH 9.5 and 20 mM dithiothreitol (DTT) was added. The RB's were extracted with a Bio-Homogenizer for 15-30 seconds and gently rocked for 2 hours at 5 degrees centigrade (5°C) to allow the protein to completely reduce and denature.

Refolding of the IL-3 muteins

The protein solution was transferred to dialysis

tubing (1000 molecular weight cut-off) and dialyzed against at least 100 volumes of 4M GnHCl - 50 mM CHES pH 8.0. The dialysis was continued overnight at 5°C while gently stirring. Subsequently dialysis was continued against at least 100 volumes of 2M GnHCl - 50 mM CHES pH 8.0 and dialyzed overnight at 5°C while gently stirring.

#### Purification of the IL-3 muteins

10 The protein solution was removed from the dialysis tubing and acidified by the addition of 40% acetonitrile (CH<sub>3</sub>CN) - 0.2% trifluoroacetic acid (TFA) to a final concentration of 20% CH<sub>3</sub>CN - 0.1% TFA. This was centrifuged (16,000 x g for 15 5 minutes) to clarify and the supernatant was loaded onto a Vydac C-18 reversed phase column (10x250 mm) available from Vydac (Hesperia, California) previously equilibrated in 20% CH<sub>3</sub>CN - 0.1% TFA. The column was eluted with a linear 20 gradient (0.2% CH<sub>3</sub>CN/minute) between 40 - 50% CH<sub>3</sub>CN - 0.1% TFA at a flow rate of 3 ml/minute while collecting 1.5 ml fractions. The fractions were analyzed by polyacrylamide gel electrophoresis (SDS-PAGE) and the appropriate 25 fractions pooled. The pooled material was dried by lyophilization or in a Speed Vac concentrator. The dry powder was reconstituted with 10 mM ammonium bicarbonate pH 7.5, centrifuged (16,000 x g for 5 minutes) to clarify and assayed for 30 protein concentration by the method of Bradford (1976) with bovine serum albumin as the standard. Such protein can be further analyzed by additional techniques such as, SDS-PAGE, electrospray mass spectrometry, reverse phase 35 HPLC, capillary zone electrophoresis, amino acid composition analysis, and ELISA (enzyme-linked immunosorbent assay).

rhIL-3 SANDWICH ELISA

The IL-3 variant protein concentrations can be determined using a sandwich ELISA based on an affinity purified polyclonal goat anti-rhIL-3. Microtiter plates (Dynatech Immulon II) were coated with 150  $\mu$ l goat-anti-rhIL-3 at a concentration of approximately 1  $\mu$ g/ml in 100 mM NaHCO<sub>3</sub>, pH 8.2. Plates were incubated overnight at room temperature in a chamber maintaining 100% humidity. Wells were emptied and the remaining reactive sites on the plate were blocked with 200  $\mu$ l of solution containing 10 mM PBS, 3% BSA and 0.05% Tween 20, pH 7.4 for 1 hour at 37° C and 100% humidity. Wells were emptied and washed 4X with 150 mM NaCl containing 0.05% Tween 20 (wash buffer). Each well then receives 150  $\mu$ l of dilution buffer (10 mM PBS containing 0.1% BSA, 0.01% Tween 20, pH 7.4), containing rhIL-3 standard, control, sample or dilution buffer alone. A standard curve was prepared with concentrations ranging from 0.125 ng/ml to 5 ng/ml using a stock solution of rhIL-3 (concentration determined by amino acid composition analysis). Plates were incubated 2.5 hours at 37° C and 100% humidity. Wells were emptied and each plate was washed 4X with wash buffer. Each well then received 150  $\mu$ l of an optimal dilution (as determined in a checkerboard assay format) of goat anti-rhIL-3 conjugated to horseradish peroxidase. Plates were incubated 1.5 hours at 37° C and 100% humidity. Wells were emptied and each plate was washed 4X with wash buffer. Each well then received 150  $\mu$ l of ABTS substrate solution (Kirkegaard and Perry). Plates were incubated at room temperature until the color of the standard wells containing 5

ng/ml rhIL-3 had developed enough to yield an absorbance between 0.5-1.0 when read at a test wavelength of 410 nm and a reference wavelength of 570 nm on a Dynatech microtiter plate reader.

5 Concentrations of immunoreactive rhIL-3 in unknown samples were calculated from the standard curve using software supplied with the plate reader.

The following examples will illustrate the invention in greater detail although it will be understood that the invention is not limited to these specific examples.

#### Example 1

##### 15 Isolation of 1-332 and 1-153 amino acid forms of Meg-CSF

A. Reverse transcriptase reaction Meg-CSF (more recently known as c-mpl ligand) sequence based on

20 Genbank accession #L33410). Human fetal liver A+ RNA was obtained from Clontech (Palo Alto, CA). The first strand cDNA reactions were carried out using a cDNA Cycle™ Kit obtained from Invitrogen (San Diego, CA).

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#### B. Polymerase chain reactions

Following the reverse transcriptase (RT) reaction, the 1-332 c-mpl ligand was amplified

30 via PCR using the oligonucleotide primers c-mplBgIII [SEQ ID NO:50] and c-mplEcoRI [SEQ ID NO:51]. Following the RT reaction, the 1-153 c-mpl ligand was amplified using the oligonucleotide primers c-mplNcoI [SEQ ID NO:52]

35 and c-mplHindIII [SEQ ID NO:53].

#### Example 2

BHK expression vector for full length c-mpl  
ligand

The full length c-mpl ligand PCR product is digested with BglII and EcoRI restriction enzymes for transfer to a mammalian expression vector. The expression vector, pMON3976, is digested with BamHI and EcoRI, which allows it to accept the BglII-EcoRI PCR fragments. pMON3976 is a derivative of pMON3359 which is a pUC18-based vector containing a mammalian expression cassette. The cassette, which includes a herpes simplex viral promoter IE110 (-800 to +120) and a SV40 late poly-adenylation (poly-A) signal, was subcloned into the pUC18 polylinker [Hippenmeyer et al., (1993)]. The original EcoRI site 5' to the promoter was removed and a new EcoRI site added 3' to the BamHI site. These unique restriction enzyme sites are located between the promoter and poly-A signal to facilitate subcloning DNA fragments as BamHI-EcoRI or BglII-EcoRI fragments in a 5' to 3' direction for transcription and translation. The resulting plasmid encodes the polypeptide with the following amino acid sequence:

Met Glu Leu Thr Glu Leu Leu Leu Val Val Met Leu Leu Leu  
Thr Ala Arg Leu Thr Leu Ser Ser Pro Ala Pro Pro Ala Cys  
Asp Leu Arg Val Leu Ser Lys Leu Leu Arg Asp Ser His Val  
Leu His Ser Arg Leu Ser Gln Cys Pro Glu Val His Pro Leu  
Pro Thr Pro Val Leu Leu Pro Ala Val Asp Phe Ser Leu Gly  
Glu Trp Lys Thr Gln Met Glu Thr Lys Ala Gln Asp Ile  
Leu Gly Ala Val Thr Leu Leu Leu Glu Gly Val Met Ala Ala  
Arg Gly Gln Leu Gly Pro Thr Cys Leu Ser Ser Leu Leu Gly  
Gln Leu Ser Gly Gln Val Arg Leu Leu Leu Gly Ala Leu Gln  
Ser Leu Leu Gly Thr Gln Leu Pro Pro Gln Gly Arg Thr Thr  
Ala His Lys Asp Pro Asn Ala Ile Phe Leu Ser Phe Gln His  
Leu Leu Arg Gly Lys Val Arg Phe Leu Met Leu Val Gly Gly

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Ser Thr Leu Cys Val Arg Arg Ala Pro Pro Thr Thr Ala Val  
 Pro Ser Arg Thr Ser Leu Val Leu Thr Leu Asn Glu Leu Pro  
 Asn Arg Thr Ser Gly Leu Leu Glu Thr Asn Phe Thr Ala Ser  
 Ala Arg Thr Thr Gly Ser Gly Leu Leu Lys Trp Gln Gln Gly  
 5 Phe Arg Ala Lys Ile Pro Gly Leu Leu Asn Gln Thr Ser Arg  
 Ser Leu Asp Gln Ile Pro Gly Tyr Leu Asn Arg Ile His Glu  
 Leu Leu Asn Gly Thr Arg Gly Leu Phe Pro Gly Pro Ser Arg  
 Arg Thr Leu Gly Ala Pro Asp Ile Ser Ser Gly Thr Ser Asp  
 Thr Gly Ser Leu Pro Pro Asn Leu Gln Pro Gly Tyr Ser Pro  
 10 Ser Pro Thr His Pro Pro Thr Gly Gln Tyr Thr Leu Phe Pro  
 Leu Pro Pro Thr Leu Pro Thr Pro Val Val Gln Leu His Pro  
 Leu Leu Pro Asp Pro Ser Ala Pro Thr Pro Thr Pro Thr Ser  
 Pro Leu Leu Asn Thr Ser Tyr Thr His Ser Gln Asn Leu Ser  
 Gln Glu Gly [SEQ ID NO:55]

15

DNA sequence [SEQ ID NO:54] codes for the  
 foregoing polypeptide.

### Example 3

#### 20 BHK expression vector for 1-153 c-mpl ligand

The 1-153 c-mpl ligand gene product was  
 digested with NcoI and HindIII restriction  
 enzymes for subcloning into pMON3934. pMON3934,  
 a mammalian expression vector, is also derived  
 25 from pMON3359, but it contains a modified human  
 IL-3 signal peptide sequence in addition to the  
 IE110 promoter and poly-A signal. The signal  
 peptide sequence is flanked by BamHI and NcoI  
 restriction enzyme sites, which facilitates  
 30 cloning and expression of genes as NcoI-HindIII  
 fragments. The HindIII site is 3' to the NcoI  
 site. The DNA sequence of the signal peptide is  
 shown below (restriction enzyme sites are  
 indicated above). The ATG (methionine) codon  
 35 within the NcoI site is in-frame with the  
 initiator ATG of the signal peptide (underlined);  
 BamHI

GGATCCACCATGAGCCGCCTGCCCGTCCTGCTCCTGCTCCAACCTCCT

MetSerArgLeuProValLeuLeuLeuLeuGlnLeuLeu

NcoI

5 GGTCCGCCCCGCCATGG [SEQ ID NO:58]  
ValArgProAlaMet [SEQ ID NO:59]

The resulting plasmid was designated pMON26448.  
The plasmid, pMON26448, encodes the following  
10 amino acid sequence:

Met Glu Leu Thr Glu Leu Leu Leu Val Val Met Leu Leu Leu  
Thr Ala Arg Leu Thr Leu Ser Ser Pro Ala Pro Pro Ala Cys  
Asp Leu Arg Val Leu Ser Lys Leu Leu Arg Asp Ser His Val  
15 Leu His Ser Arg Leu Ser Gln Cys Pro Glu Val His Pro Leu  
Pro Thr Pro Val Leu Leu Pro Ala Val Asp Phe Ser Leu Gly  
Glu Trp Lys Thr Gln Met Glu Glu Thr Lys Ala Gln Asp Ile  
Leu Gly Ala Val Thr Leu Leu Leu Glu Gly Val Met Ala Ala  
Arg Gly Gln Leu Gly Pro Thr Cys Leu Ser Ser Leu Leu Gly  
20 Gln Leu Ser Gly Gln Val Arg Leu Leu Leu Gly Ala Leu Gln  
Ser Leu Leu Gly Thr Gln Leu Pro Pro Gln Gly Arg Thr Thr  
Ala His Lys Asp Pro Asn Ala Ile Phe Leu Ser Phe Gln His  
Leu Leu Arg Gly Lys Val Arg Phe Leu Met Leu Val Gly Gly  
Ser Thr Leu Cys Val Arg [SEQ ID NO:56]

25  
DNA sequence [SEQ ID NO:54] codes the foregoing  
amino acid sequence.

For secreted 1-153 c-mpl ligand, the N-  
30 terminal sequence should be SerProAla..., like  
that described elsewhere [de Sauvage et al.,  
(1994)]. For the 1-332 c-mpl ligand, which  
contains its own secretion signal, it also should  
be cleaved to leave SerProAla... on the N-  
35 terminus. Therefore, the numbering system  
assumes that SerProAla... are the first three  
amino acids on either protein.



AML Proliferation Assay for Bioactive Human  
Interleukin-3

The factor-dependent cell line AML 193 was  
5 obtained from the American Type Culture Collection  
(ATCC, Rockville, MD). This cell line, established  
from a patient with acute myelogenous leukemia, was a  
growth factor dependent cell line which displayed  
enhanced growth in GM/CSF supplemented medium  
10 (Lange, B., et al., (1987); Valtieri, M., et al.,  
(1987)). The ability of AML 193 cells to proliferate in  
the presence of human IL-3 has also been documented.  
(Santoli, D., et al., (1987)). A cell line variant was  
used, AML 193 1.3, which was adapted for long term  
15 growth in IL-3 by washing out the growth factors and  
starving the cytokine dependent AML 193 cells for  
growth factors for 24 hours. The cells were then  
replated at  $1 \times 10^5$  cells/well in a 24 well plate in  
media containing 100 U/ml IL-3. It took approximately  
20 2 months for the cells to grow rapidly in IL-3. These  
cells were maintained as AML 193 1.3 thereafter by  
supplementing tissue culture medium (see below) with  
human IL-3.

AML 193 1.3 cells were washed 6 times in cold  
25 Hanks balanced salt solution (HBSS, Gibco, Grand  
Island, NY) by centrifuging cell suspensions at  $250 \times g$   
for 10 minutes followed by decantation of supernatant.  
Pelleted cells were resuspended in HBSS and the  
procedure was repeated until six wash cycles were  
30 completed. Cells washed six times by this procedure  
were resuspended in tissue culture medium at a density  
ranging from  $2 \times 10^5$  to  $5 \times 10^5$  viable cells/ml. This  
medium was prepared by supplementing Iscove's modified  
Dulbecco's Medium (IMDM, Hazelton, Lenexa, KS) with  
35 albumin, transferrin, lipids and 2-mercaptoethanol.  
Bovine albumin (Boehringer-Mannheim, Indianapolis, IN)  
was added at 500  $\mu g/ml$ ; human transferrin (Boehringer-

Mannheim, Indianapolis, IN) was added at 100  $\mu\text{g}/\text{ml}$ ; soybean lipid (Boehringer-Mannheim, Indianapolis, IN) was added at 50  $\mu\text{g}/\text{ml}$ ; and 2-mercaptoethanol (Sigma, St. Louis, MO) was added at  $5 \times 10^{-5} \text{ M}$ .

- 5        Serial dilutions of human interleukin-3 or human interleukin-3 variant protein (hIL-3 mutein) were made in triplicate series in tissue culture medium supplemented as stated above in 96 well Costar 3596 tissue culture plates. Each well contained 50  $\mu\text{l}$  of
- 10        medium containing interleukin-3 or interleukin-3 variant protein once serial dilutions were completed. Control wells contained tissue culture medium alone (negative control). AML 193 1.3 cell suspensions prepared as above were added to each well by pipetting
- 15        50  $\mu\text{l}$  ( $2.5 \times 10^4$  cells) into each well. Tissue culture plates were incubated at  $37^\circ\text{C}$  with 5%  $\text{CO}_2$  in humidified air for 3 days. On day 3, 0.5  $\mu\text{Ci}$   $^3\text{H}$ -thymidine (2 Ci/mM, New England Nuclear, Boston, MA) was added in 50  $\mu\text{l}$  of tissue culture medium. Cultures were incubated
- 20        at  $37^\circ\text{C}$  with 5%  $\text{CO}_2$  in humidified air for 18-24 hours. Cellular DNA was harvested onto glass filter mats (Pharmacia LKB, Gaithersburg, MD) using a TOMTEC cell harvester (TOMTEC, Orange, CT) which utilized a water wash cycle followed by a 70% ethanol wash cycle.
- 25        Filter mats were allowed to air dry and then placed into sample bags to which scintillation fluid (Scintiverse II, Fisher Scientific, St. Louis, MO or BetaPlate Scintillation Fluid, Pharmacia LKB, Gaithersburg, MD) was added. Beta emissions of samples
- 30        from individual tissue culture wells were counted in a LKB Betaplate model 1205 scintillation counter (Pharmacia LKB, Gaithersburg, MD) and data was expressed as counts per minute of  $^3\text{H}$ -thymidine incorporated into cells from each tissue culture well.
- 35        Activity of each human interleukin-3 preparation or human interleukin-3 variant preparation was quantitated by measuring cell proliferation ( $^3\text{H}$ -thymidine

incorporation) induced by graded concentrations of interleukin-3 or interleukin-3 variant. Typically, concentration ranges from 0.05 pM - 105 pM were quantitated in these assays. Activity was determined by measuring the dose of interleukin-3 or interleukin-3 variant which provides 50% of maximal proliferation [ $EC_{50} = 0.5 \times$  (maximum average counts per minute of  $^3H$ -thymidine incorporated per well among triplicate cultures of all concentrations of interleukin-3 tested - background proliferation measured by  $^3H$ -thymidine incorporation observed in triplicate cultures lacking interleukin-3]. This  $EC_{50}$  value is also equivalent to 1 unit of bioactivity. Every assay was performed with native interleukin-3 as a reference standard so that relative activity levels could be assigned.

#### Methylcellulose Assay

This assay provides a reasonable approximation of the growth activity of colony stimulating factors to stimulate normal bone marrow cells to produce different types of hematopoietic colonies in vitro (Bradley et al., 1966, Pluznik et al., 1965).

#### 25 Methods

Approximately 30 ml of fresh, normal, healthy bone marrow aspirate are obtained from individuals. Under sterile conditions samples are diluted 1:5 with a 1X PBS (#14040.059 Life Technologies, Gaithersburg, MD.) solution in a 50 ml conical tube (#25339-50 Corning, Corning MD). Ficoll (Histopaque-1077 Sigma H-8889) is layered under the diluted sample and centrifuged, 300 x g for 30 min. The mononuclear cell band is removed and washed two times in 1X PBS and once with 1% BSA PBS (CellPro Co., Bothel, WA). Mononuclear cells are counted and CD34+ cells are selected using the Ceprate LC (CD34) Kit (CellPro Co., Bothel, WA) column. This

fractionation is performed since all stem and progenitor cells within the bone marrow display CD34 surface antigen. Alternatively whole bone marrow or peripheral blood may be used.

- 5 Cultures are set up in triplicate wells with a final volume of 0.1 ml in 48 well tissue culture plates (#3548 CoStar, Cambridge, MA). Culture medium is purchased from Terry Fox Labs. (HCC-4330 medium (Terry
- 10 Fox Labs, Vancouver, B.C., Canada)). 600-1000 CD34+ cells are added per well. Native IL-3 and IL-3 variants are added to give final concentrations ranging from .001nM-10nM. G-CSF and GM-CSF and C-Kit ligand are added at a final concentration of 0.1nM. Native
- 15 IL-3 and IL-3 variants are supplied in house. C-Kit Ligand (#255-CS), G-CSF (#214-CS) and GM-CSF (#215-GM) are purchased from R&D Systems (Minneapolis, MN). Cultures are resuspended using an Eppendorf repeater and 0.1 ml is dispensed per well. Control (baseline
- 20 response) cultures received no colony stimulating factors. Positive control cultures received conditioned media (PHA stimulated human cells: Terry Fox Lab. H2400). Cultures are incubated at 37°C, 5% CO<sub>2</sub> in humidified air.
- 25 Hematopoietic colonies which are defined as greater than 50 cells are counted on the day of peak response (days 10-11) using a Nikon inverted phase microscope with a 40x objective combination. Groups of cells containing fewer than 50 cells are referred to as
- 30 clusters. Alternatively colonies can be identified by spreading the colonies on a slide and stained or they can be picked, resuspended and spun onto cytopsin slides for staining.

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EXAMPLE 4

The synergistic effect of the IL-3 variant, pMON13288, with G-CSF was evaluated in the methylcellulose assay compared to that of native IL-3 with G-CSF. G-CSF was added to each culture at a concentration of 0.1nM.

5 Native IL-3 and the IL-3 variant, pMON13288, were added at final concentrations ranging from 0.001nM to 10nM. Colonies were counted on the day of peak response (days 10-11). pMON13288 activates more progenitor cells than native IL-3 (Figure 2). Native IL-3 plus G-CSF and the

10 IL-3 variant, pMON13288, plus G-CSF resulted in an increase in colony number greater than the additive effect of the individual proteins alone (Figure 2). The synergistic effect of the IL-3 variant, pMON13288, with G-CSF was greater than that of native IL-3 with G-CSF.

15 Hematopoietic colony forming activity of the IL-3 variant, pMON13288, was multi-lineage whereas G-CSF alone activates primarily granulocytic cells at molar equivalent doses. In Figure 2 the concentration of IL-3 is plotted versus the colony counts per 100,000

20 starting CD34+ cells.

#### EXAMPLE 5

The synergistic effect of the IL-3 variant, pMON13288, with GM-CSF was evaluated in the methylcellulose assay compared to that of native IL-3 with GM-CSF. GM-CSF was added to each culture at a concentration of 0.1nM.

25 Native IL-3 and the IL-3 variant, pMON13288, were added at final concentrations ranging from 0.001nM to 10nM. Colonies were counted on the day of peak response (days 10-11). pMON13288 activates more progenitor cells than native IL-3 (Figure 3). Native IL-3 plus GM-CSF and the

30 IL-3 variant, pMON13288, plus GM-CSF resulted in an increase in colony number greater than the effect of the individual proteins alone (Figure 3). The synergistic effect of the IL-3 variant, pMON13288, with GM-CSF was greater than that of native IL-3 with GM-

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CSF. In Figure 3 the concentration of IL-3 is plotted versus the colony counts per 100,000 starting CD34+ cells.

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EXAMPLE 6

Methylcellulose assays for native IL-3, pMON5873, were carried out in methylcellulose, with or without EPO. Although EPO increased the total number of colonies, it didn't appear to increase CFU-GM, which are of more interest. The presence of erythroid colonies also made scoring more subjective, because one must distinguish between multifocal BFU-E vs several closely associated single focus CFU-E. EPO also gave a high background of total colonies, which would tend to obscure the dose dependent response of CFU-GM to other CSFs.

Methylcellulose assays comparing native IL-3 (pMON5873) to the IL-3 variant, pMON13288 were carried out in the presence of stem cell factor (SCF) without EPO. SCF gives no background response in these assays, but appears to increase the dose dependent response of CFU-GM to both native IL-3 (pMON5873) and the IL-3 variant, pMON13288. This result is consistent with reports in the literature of in vitro synergies between IL-3 and SCF (Migliaccio et al., 1992). The IL-3 variant, pMON13288, appears to be more potent in these assays, and gives a greater maximum number of colonies (also larger) than native IL-3 (pMON5873).

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Human Cord Blood Hemopoietic Growth Factor Assays

Bone marrow cells are traditionally used for in vitro assays of hematopoietic colony stimulating factor (CSF) activity. However, human bone marrow is not always available, and there is considerable variability between donors. Umbilical cord blood is comparable to

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bone marrow as a source of hematopoietic stem cells and progenitors (Broxmeyer et al., 1992; Mayani et al., 1993). In contrast to bone marrow, cord blood is more readily available on a regular basis. There is also a potential to reduce assay variability by pooling cells obtained fresh from several donors, or to create a bank of cryopreserved cells for this purpose. By modifying the culture conditions, and/or analyzing for lineage specific markers, it should be possible to assay specifically for granulocyte / macrophage colonies (CFU-GM), for megakaryocyte CSF activity, or for high proliferative potential colony forming cell (HPP-CFC) activity.

#### 15 METHODS

Mononuclear cells (MNC) are isolated from cord blood within 24 hrs of collection, using a standard density gradient (1.077g/ml Histopaque). Cord blood MNC have been further enriched for stem cells and progenitors by several procedures, including immunomagnetic selection for CD14-, CD34+ cells; panning for SBA-, CD34+ fraction using coated flasks from Applied Immune Science (Santa Clara, CA); and CD34+ selection using a CellPro (Bothell, WA) avidin column. Either freshly isolated or cryopreserved CD34+ cell enriched fractions are used for the assay. Duplicate cultures for each serial dilution of sample (concentration range from 1pM to 1204pM) are prepared with 1x10<sup>4</sup> cells in 1ml of .9% methycellulose containing medium without additional growth factors (Methocult H4230 from Stem Cell Technologies, Vancouver, BC.). In some experiments, Methocult H4330 containing erythropoietin (EPO) was used instead of Methocult H4230, or Stem Cell Factor (SCF), 50ng/ml (Biosource International, Camarillo, CA) was added. After culturing for 7-9 days, colonies containing >30 cells are counted. In order to rule out subjective bias in scoring, assays are scored blind.

Analysis of c-mpl ligand proliferative activity

## 5 METHODS

## 1. Bone marrow proliferation assay

## a. CD34+ Cell Purification:

Between 15-20 ml bone marrow aspirates were  
10 obtained from normal allogeneic marrow donors  
after informed consent. Cells were diluted 1:3  
in phosphate buffered saline (PBS, Gibco-BRL), 30  
ml were layered over 15 ml Histopaque-1077  
(Sigma) and centrifuged for 30 minutes at 300  
15 RCF. The mononuclear interface layer was  
collected and washed in PBS. CD34+ cells were  
enriched from the mononuclear cell preparation  
using an affinity column per manufacturers  
instructions (CellPro, Inc, Bothell WA). After  
20 enrichment, the purity of CD34+ cells was 70% on  
average as determined by using flow cytometric  
analysis using anti CD34 monoclonal antibody  
conjugated to fluorescein and anti CD38  
conjugated to phycoerythrin (Becton Dickinson,  
25 San Jose CA).

Cells were resuspended at 40,000 cells/ml in  
X-Vivo 10 media (Bio-Whittaker, Walkersville, MD)  
and 1 ml was plated in 12-well tissue culture  
plates (Costar). The growth factor rhIL-3 was  
30 added at 100 ng/ml (pMON5873) was added to some  
wells. hIL3 variant, pMON13288 was used at 10  
ng/ml or 100 ng/ml. Conditioned media from BHK  
cells transfected with plasmid encoding c-mpl  
ligand were tested by addition of 100  $\mu$ l of  
35 supernatant added to 1 ml cultures (approximately  
a 10% dilution). Cells were incubated at 37°C  
for 8-14 days at 5% CO<sub>2</sub> in a 37°C humidified



incubator.

b. Cell Harvest and Analysis:

At the end of the culture period a total  
5 cell count was obtained for each condition. For  
fluorescence analysis and ploidy determination  
cells were washed in megakaryocyte buffer (MK  
buffer, 13.6 mM Sodium Citrate, 1 mM  
Theophylline, 2.2  $\mu$ M PGE1, 11 mM Glucose, 3% w/v  
10 BSA, in PBS, pH 7.4,) [See Tomer et al., Blood  
70, 1987, pp. 1736-42] resuspended in 500  $\mu$ l of  
MK buffer containing anti-CD41a FITC antibody  
(1:200, AMAC, Westbrook, ME) and washed in MK  
buffer. For DNA analysis cells were permeablized  
15 in MK buffer containing 0.5% Tween 20 (Fisher,  
Fair Lawn NJ) for 20 min. on ice followed by  
fixation in 0.5% Tween-20 and 1% paraformaldehyde  
(Fisher Chemical) for 30 minutes followed by  
incubation in Propidium Iodide (Calbiochem, La  
20 Jolla Ca) (50  $\mu$ g/ml) with RNA-ase (400 U/ml) in  
55% v/v MK buffer (200mOsm) for 1-2 hours on ice.  
Cells were analyzed on a FACScan or Vantage flow  
cytometer (Becton Dickinson, San Jose, CA).  
Green fluorescence (CD41a-FITC) was collected  
25 along with linear and log signals for red  
fluorescence (PI) to determine DNA ploidy. All  
cells were collected to determine the percent of  
cells that were CD41+. Data analysis was  
performed using software by LYSIS (Becton  
30 Dickinson, San Jose, CA). Percent of cells  
expressing the CD41 antigen was obtained from  
flow cytometry analysis(Percent). Absolute (Abs)  
number of CD41+ cells/ml was calculated by:  
(Abs)=(Cell Count)\*(Percent)/100.

35

2. Megakaryocyte fibrin clot assay.

- CD34+ enriched population were isolated as described above. Cells were suspended at 25,000 cells/ml with/without cytokine(s) in a media
- 5 consisting of a base Iscoves IMDM media supplemented with 0.3% BSA, 0.4mg/ml apo-transferrin, 6.67 $\mu$ M FeCl<sub>2</sub>, 25 $\mu$ g/ml CaCl<sub>2</sub>, 25 $\mu$ g/ml L-asparagine, 500 $\mu$ g/ml E-amino-n-caproic acid and Penicillin/Streptomycin. Prior to plating into
- 10 35mm plates, thrombin was added (0.25 Units/ml) to initiate clot formation. Cells were incubated at 37°C for 13 days at 5% CO<sub>2</sub> in a 37°C humidified incubator.
- 15 At the end of the culture period plates were fixed with Methanol:Acetone (1:3), air dried and stored at -20°C until staining. A peroxidase immunocytochemistry staining procedure was used (Zymed, Histostain-SP. San Francisco, CA) using a
- 20 cocktail of primary monoclonal antibodies consisting of anti CD41a, CD42 and CD61. Colonies were counted after staining and classified as negative, CFU-MK (small colonies, 1-2 foci and less than approx. 25 cells), BFU-MK
- 25 (large, multi-foci colonies with > 25 cells) or mixed colonies (mixture of both positive and negative cells).

#### Example 7

30

#### Co-administration of hIL-3 variant, pMON13288 and c-mpl ligand (Meg-CSF) in liquid culture

- Co-administration of hIL-3 variant, pMON13288 and
- 35 c-mpl ligand (Meg-CSF) has a more than additive effect on megakaryocyte expansion than either cytokine alone in the liquid culture assay

CD34+ cells were isolated as described in the methods section. The assay was set up as described in the methods section except that

5 cells were plated at 4000 cells/100 $\mu$ l in a 96-well plate. pMON26448 or a mock transfectant was evaluated by adding 10  $\mu$ l to each well (10% final). Supernatant from transfected BHK cells were tested +/- hIL3 variant, pMON13288 (10

10 ng/ml). At day 10 phenotypic analysis was performed by flow cytometry. Supernatant from pMON26448 induced selective expansion of CD41a+ cells. Total cell number increased from the 4000 cells plated to 22,000 at the end of the assay

15 (Table 1). Addition of hIL3 variant, pMON13288 alone increased total cell numbers (19,000 cells at end of assay) with 17% of cells expressing CD41a. Combination of pMON26448 with hIL3 variant, pMON13288 resulted in 56% of cells

20 expressing CD41a. Total cell expansion in the combination assay was more than additive with 86,000 cells/well. Both the increased total cell number and the higher percentage of cells expressing CD41a resulted in an increase in total

25 number CD41+ cells that also was more than additive as compared to either cytokine alone (48,000 vs. 3,320 and 18,480).

Table 1

30

Cytokine Treatment	Cells/Well	%CD41a Positive	# CD41+ Cells/Well
pMON13288	19,000	17	3,230
pMON26448	22,000	84	18,480

100

pMON26448	86,000	56	48,160
+ pMON13288			

Example 8

5 Co-administration of hIL-3 variant, pMON13288, and c-mpl ligand (Meg-CSF) in liquid culture

The co-administration of hIL-3 variant, pMON13288, and c-mpl ligand (Meg-CSF) has a more  
 10 than additive effect on megakaryocyte expansion than either cytokine alone in the liquid culture assay

In another experiment CD34+ cells were isolated  
 15 from Human bone marrow using a CD34 affinity column (Cellpro). Purified CD34+ cells were resuspended in X-Vivo tissue culture media at 40,000 cells/ml. pMON26448 or a mock transfectant (10%) was evaluated with/without hIL3 variant,  
 20 pMON13288 or native IL3. At day 8 phenotypic analysis was done using flow cytometry. As was seen in the table below (Table 2a-c). IL3, both concentrations of hIL3 variant, pMON13288 and pMON26448 increased total cell number  
 25 substantially. Combination of cytokines further expanded cell populations. pMON26448 increased the percent of CD41+ cells from 2% in the control group to 35%. IL3 or hIL3 variant, pMON13288 increased the percent of CD41+ cells modestly  
 30 (from 2% to 5%). Combining pMON26448 with IL3 or hIL3 variant, pMON13288 resulted in a more than additive number of CD41+ cells as compared to the sum of either cytokine alone (Table 2c).

Table 2(a-c)

## a. Total Cells/Well

Cytokine treatment	Media	IL-3 (100ng/ml)	pMON13288 (10ng/ml)	pMON13288 (100ng/ml)
Media	30,000	112,000	275,000	150,000
Mock	10,000	153,000	235,000	260,000
pMON26448	135,000	655,000	625,000	500,000

## 5 b. %CD41a+

Cytokine treatment	Media	IL-3 (100ng/ml)	pMON13288 (10ng/ml)	pMON13288 (100ng/ml)
Media	2	7	5	5
Mock	2	14	5	9
pMON26448	35	35	28	29

## c. Total CD41a+ Cells

Cytokine treatment	Media	IL-3 (100ng/ml)	pMON13288 (10ng/ml)	pMON13288 (100ng/ml)
Media	600	7,840	13,750	7,500
Mock	200	21,420	11,750	23,400
pMON26448	47,250	229,250	175,000	145,000

10

Example 9

Co-administration of hIL-3 variant, pMON13288, and c-mpl ligand (Meg-CSF) in fibrin clot assay

15

The co-administration of hIL-3 variant, pMON13288, and c-mpl ligand (Meg-CSF) has a more than additive effect on megakaryocyte than either cytokine alone.

20

Fibrin clot cultures were set up as described in methods section. pMON26448 is the 1-153 form of

c-mpl ligand (Meg-CSF). Incubation in the presence of hIL3 variant, pMON13288 gave rise to colonies that were predominantly negative for megakaryocyte markers (86/114, (Table 3)) except  
5 for number of small CFU-MK colonies (23/114). pMON26448 alone gave rise primarily to CFU-MK colonies (172/175) with only a few number of negative colonies (3/175). Combination of hIL3 variant, pMON13288 and pMON26448 gave rise to a  
10 large number of positive colonies (295/414) that were predominantly of the BFU-MK morphology. There were a negative colonies as well (119/414). Total number of positive colonies with co-administration was more than additive than with  
15 either cytokine alone.

Table 3.

Colonies/Well					
Cytokine treatment	Negative	CFU-MK	BFU-MK	Mixed	Total Colonies
pMON13288	86	23	0	5	114
pMON26448	3	73	98	1	175
pMON26448 + pMON13288	119	29	244	22	414
Colonies/100,000 plated					
Cytokine treatment	Negative	CFU-MK	BFU-MK	Mixed	Total Colonies
pMON13288	344	92	0	20	456
pMON26448	12	292	392	4	700
pMON26448 + pMON13288	476	116	976	88	1656

5

IL-3 mediated sulfidoleukotriene release from human mononuclear cells

The following assay was used to measure IL-3 mediated sulfidoleukotriene release from human mononuclear cells.

10

Heparin-containing human blood was collected and layered onto an equal volume of Ficoll-Paque

104

(Pharmacia # 17-0840-02) ready to use medium (density 1.077 g/ml.). The Ficoll was warmed to room temperature prior to use and clear 50 ml polystyrene tubes were utilized. The Ficoll gradient was spun at 300 x g for 30 minutes at room temperature using a H1000B rotor in a Sorvall RT6000B refrigerated centrifuge. The band containing the mononuclear cells was carefully removed, the volume adjusted to 50 mls with Dulbecco's phosphate-buffered saline (Gibco Laboratories cat. # 310-4040PK), spun at 400 x g for 10 minutes at 4°C and the supernatant was carefully removed. The cell pellet was washed twice with HA Buffer [ 20 mM Hepes (Sigma # H-3375), 125 mM NaCl (Fisher # S271-500), 5 mM KCl (Sigma # P-9541), 0.5 mM glucose (Sigma # G-5000), 0.025% Human Serum Albumin (Calbiochem # 126654) and spun at 300 x g, 10 min., 4°C. The cells were resuspended in HACM Buffer (HA buffer supplemented with 1 mM CaCl<sub>2</sub> (Fisher # C79-500) and 1 mM MgCl<sub>2</sub> (Fisher # M-33) at a concentration of 1 x 10<sup>6</sup> cells/ml and 180 µl were transferred into each well of 96 well tissue culture plates. The cells were allowed to acclimate at 37°C for 15 minutes. The cells were primed by adding 10 µls of a 20 X stock of various concentrations of cytokine to each well (typically 100000, 20000, 4000, 800, 160, 32, 6.4, 1.28, 0 fM IL3). The cells were incubated for 15 minutes at 37°C. Sulfidoleukotriene release was activated by the addition of 10 µls of 20 X (1000 nM) fmet-leu-phe (Calbiochem # 344252) final concentration 50nM FMLP and incubated for 10 minutes at 37°C. The plates were spun at 350 x g at 4°C for 20 minutes. The supernatants were removed and assayed for sulfidoleukotrienes using Cayman's Leukotriene C4 EIA kit (Cat. #420211) according



to manufacturers' directions. Native (15-125)hIL-3 was run as a standard control in each assay.

Further details known to those skilled in the art may be found in T. Maniatis, et al., Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory (1982) and references cited therein, incorporated herein by reference; and in J. Sambrook, et al., Molecular Cloning, A Laboratory Manual, 2nd edition, Cold Spring Harbor Laboratory (1989) and references cited therein, incorporated herein by reference.

Amino acids are shown herein by standard one letter or three letter abbreviations as follows:

15	Abbreviated Designation		Amino Acid
	A	Ala	Alanine
	C	Cys	Cysteine
20	D	Asp	Aspartic acid
	E	Glu	Glutamic acid
	F	Phe	Phenylalanine
	G	Gly	Glycine
	H	His	Histidine
25	I	Ile	Isoleucine
	K	Lys	Lysine
	L	Leu	Leucine
	M	Met	Methionine
	N	Asn	Asparagine
30	P	Pro	Proline
	Q	Gln	Glutamine
	R	Arg	Arginine
	S	Ser	Serine
	T	Thr	Threonine
35	V	Val	Valine
	W	Trp	Tryptophan
	Y	Tyr	Tyrosine

Additional details may be found in co-  
pending United States Patent Application Serial  
number PCT/US93/11197 which is hereby  
incorporated by reference in its entirety as if  
5 written herein.

All references, patents or applications  
cited herein are incorporated by reference in  
their entirety as if written herein.

10 Various other examples will be apparent to  
the person skilled in the art after reading the  
present disclosure without departing from the  
spirit and scope of the invention. It is  
intended that all such other examples be included  
15 within the scope of the appended claims.

TABLE 4  
OLIGONUCLEOTIDES

c-*mplBgl*III  
20 CATGGCAAGATCTCCGGCCAGAATGGAGCTGACTGA [SEQ ID NO:50]

c-*mplEco*RI  
AATAGCTGAATTCTTACCCTTCCTGAGACAGATT [SEQ ID NO:51]

25 c-*mplNco*I  
ACGTCCATGGCNTCNCNCNCNCCTGCTTGTGACCTCCGAGTC  
[SEQ ID NO:52]

(where N= G, C, T or A)

30 c-*mplHind*III  
TGACAAGCTTACCTGACGCGAGAGGGTGGACCT [SEQ ID NO:53]

TABLE 5  
DNA SEQUENCES

35 1-153 c-*mpl* ligand

ATGGCGTCTC CGGCGCCGCC TGCTTGTGAC CTCCGAGTCC TCAGTAACT

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GCTTCGTGAC TCCCATGTCC TTCACAGCAG ACTGAGCCAG TGCCACAGAG  
 TTCACCCCTT GCCTACACCT GTCCTGCTGC CTGCTGTGGA CTTTAGCTTG  
 GGAGAAATGA AAACCCAGAT GGAGGAGACC AAGGCACAGG ACATTCTGGG  
 AGCAGTGACC CTTCCTGCTGG AGGGAGTGAT GGCAGCACGG GGACAACTGG  
 5 GACCCACTTG CCTCTCATCC CTCCTGGGGC AGCTTTCTGG ACAGGTCCGT  
 CTCCTCCTTG GGGCCCTGCA GAGCCTCCTT GGAACCCAGC TTCCTCCACA  
 GGGCAGGACC ACAGCTCACA AGGATCCCAA TGCCATCTTC CTGAGCTTCC  
 AACACCTGCT CCGAGGAAAG GTGCGTTTCC TGATGCTTGT AGGAGGGTCC  
 ACCCTCTGCG TCAGG [SEQ ID NO:54]

10

Full length c-mpl ligand

ATGGAGCTGA CTGAATTGCT CCTCGTGGTC ATGCTTCTCC TAACTGCAAG  
 GCTAACGCTG TCCAGCCCGG CTCCTCCTGC TTGTGACCTC CGAGTCCTCA  
 15 GTAAACTGCT TCGTGACTCC CATGTCCCTC ACAGCAGACT GAGCCAGTGC  
 CCAGAGGTTT ACCCTTTGCC TACACCTGTC CTGCTGCCCTG CTGTGGAGTT  
 TAGCTTGGGA GAATGGAAAA CCCAGATGGA GGAGACCAAG GCACAGGACA  
 TTCTGGGAGC AGTGACCCCTT CTGCTGGAGG GAGTGATGCG AGCACGGGGA  
 CAACTGGGAC CCACTTGCCCT CTCATCCCTC CTGGGGCAGC TTCTTGGA  
 20 GGTCCGCTCT CTCCTTGGGG CCCTGCAGAG CCTCCTTGGA ACCCAGCTTC  
 CTCCACAGGG CAGGACCACA GCTACAAGG ATCCCAATGC CATCTTCCCTG  
 AGCTTCCAAC ACCTGCTCCG AGGAAAGGTG CGTTTCCTGA TGCTTGATAG  
 AGGGTCCACC CTCTGCGTCA GCGGGGCCCC ACCCACCACA GCTGTCCCAA  
 GCAGAACCTC TCTAGTCTCT ACACCTGAACG AGCTCCCAA CAGGACTTCT  
 25 GGATTGTTGG AGACAACTT CACTGCCCTA GCCAGAATA CTGGCTCTGG  
 GCTTCTGAAG TGGCAGCAGG GATTCAGAGC CAAGATTCCT GGTCTGCTGA  
 ACCAAACCTC CAGGTCCCTG GACCAAATCC CCGGATACCT GAACAGGATA  
 CACGAACCTT TGAATGGAAC TCGTGGACTC TTTCTTGGAC CCTCAGCAG  
 GACCCTAGGA GCGCCGGACA TTTCTCAGG AACATCAGAC ACAGGCTCCC  
 30 TGCCACCCAA CCTCCAGCCT GGATATTCTC CTTCCTCCAA CCATCCTCCT  
 ACTGGACAGT ATACGCTCTT CCCTCTTCCA CCCACCTTGC CCACCCCTGT  
 GGTCCAGCTC CACCCCTGTC TTCTGAGGCC TTCTGCTCCA ACGCCACCC  
 CTACCAGCCC TCTTCTAAAC ACATCCTACA CCCACTCCCA GAATCTGTCT  
 CAGGAAGGG [SEQ ID NO:57]

35

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Zoller, M.J. and Smith, M. Oligonucleotide-directed Mutagenesis: A simple method using two oligonucleotide primers and a single-stranded DNA template. DNA, 3: 479 (1984).

## SEQUENCE LISTING

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  - (D) SOFTWARE: PatentIn Release #1.0, Version #1.25
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  - (A) APPLICATION NUMBER:
  - (B) FILING DATE: 21-DEC-2001
  - (C) CLASSIFICATION:
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  - (A) APPLICATION NUMBER: US 08/193,373
  - (B) FILING DATE: 04-FEB-1994
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## (2) INFORMATION FOR SEQ ID NO:1:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 133 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 1
  - (D) OTHER INFORMATION: /note= "Met- may or may not precede the amino acid in position 1"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 17
  - (D) OTHER INFORMATION: /note= "Xaa at position 17 is Ser, Lys, Gly, Asp, Met, Gln, or Arg"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 18
  - (D) OTHER INFORMATION: /note= "Xaa at position 18 is Asn, His, Leu, Ile, Phe, Arg, or Gln"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 19
  - (D) OTHER INFORMATION: /note= "Xaa at position 19 is Met, Phe, Ile, Arg, Gly, Ala, or Cys"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 20
  - (D) OTHER INFORMATION: /note= "Xaa at position 20 is Ile, Cys, Gln, Glu, Arg, Pro, or Ala"
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- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 21
  - (D) OTHER INFORMATION: /note= "Xaa at position 21 is Asp, Phe, Lys, Arg, Ala, Gly, Glu, Gln, Asn, Thr, Ser, or Val"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 22
  - (D) OTHER INFORMATION: /note= "Xaa at position 22 is Glu, Trp, Pro, Ser, Ala, His, Asp, Asn, Gln, Leu, Val, or Gly"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 23
  - (D) OTHER INFORMATION: /note= "Xaa at position 23 is Ile, Val, Ala, Leu, Gly, Trp, Lys, Phe, Ser, or Arg"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 24
  - (D) OTHER INFORMATION: /note= "Xaa at position 24 is Ile, Gly, Val, Arg, Ser, Phe, or Leu"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 25

- (D) OTHER INFORMATION: /note= "Xaa at position 25 is Thr, His, Gly, Gln, Arg, Pro, or Ala"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 26  
(D) OTHER INFORMATION: /note= "Xaa at position 26 is His, Thr, Phe, Gly, Arg, Ala, or Trp"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 27  
(D) OTHER INFORMATION: /note= "Xaa at position 27 is Leu, Gly, Arg, Thr, Ser, or Ala"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 28  
(D) OTHER INFORMATION: /note= "Xaa at position 28 is Lys, Arg, Leu, Gln, Gly, Pro, Val, or Trp"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 29  
(D) OTHER INFORMATION: /note= "Xaa at position 29 is Gln, Asn, Leu, Pro, Arg, or Val"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 30  
(D) OTHER INFORMATION: /note= "Xaa at position 30 is Pro, His, Thr, Gly, Asp, Gln, Ser, Leu, or Lys"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 31  
(D) OTHER INFORMATION: /note= "Xaa at position 31 is Pro, Asp, Gly, Ala, Arg, Leu, or Gln"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 32  
(D) OTHER INFORMATION: /note= "Xaa at position 32 is Leu, Val, Arg, Gln, Asn, Gly, Ala, or Glu"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 33  
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- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
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(D) OTHER INFORMATION: /note= "Xaa at position 34 is Leu, Val, Gly, Ser, Lys, Glu, Gln, Thr, Arg, Ala, Phe, Ile, or Met"
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(A) NAME/KEY: Modified-site  
(B) LOCATION: 35  
(D) OTHER INFORMATION: /note= "Xaa at position 35 is Leu, Ala, Gly, Asn, Pro, Gln, or Val"
- (ix) FEATURE:  
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(B) LOCATION: 36

- (D) OTHER INFORMATION: /note= "Xaa at position 36 is Asp, Leu, or Val"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 37  
(D) OTHER INFORMATION: /note= "Xaa at position 37 is Phe, Ser, Pro, Trp, or Ile"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 38  
(D) OTHER INFORMATION: /note= "Xaa at position 38 is Asn, or Ala"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 40  
(D) OTHER INFORMATION: /note= "Xaa at position 40 is Leu, Trp, or Arg"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 41  
(D) OTHER INFORMATION: /note= "Xaa at position 41 is Asn, Cys, Arg, Leu, His, Met, or Pro"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 42  
(D) OTHER INFORMATION: /note= "Xaa at position 42 is Gly, Asp, Ser, Cys, Asn, Lys, Thr, Leu, Val, Glu, Phe, Tyr, Ile, Met, or Ala"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 43  
(D) OTHER INFORMATION: /note= "Xaa at position 43 is Glu, Asn, Tyr, Leu, Phe, Asp, Ala, Cys, Gln, Arg, Thr, Gly, or Ser"
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(A) NAME/KEY: Modified-site  
(B) LOCATION: 44  
(D) OTHER INFORMATION: /note= "Xaa at position 44 is Asp, Ser, Leu, Arg, Lys, Thr, Met, Trp, Glu, Asn, Gln, Ala, or Pro"
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(A) NAME/KEY: Modified-site  
(B) LOCATION: 45  
(D) OTHER INFORMATION: /note= "Xaa at position 45 is Gln, Pro, Phe, Val, Met, Leu, Thr, Lys, Trp, Asp, Asn, Arg, Ser, Ala, Ile, Glu, or His"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 46  
(D) OTHER INFORMATION: /note= "Xaa at position 46 is Asp, Phe, Ser, Thr, Cys, Glu, Asn, Gln, Lys, His, Ala, Tyr, Ile, Val, or Gly"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 47  
(D) OTHER INFORMATION: /note= "Xaa at position 47 is Ile, Gly, Val, Ser, Arg, Pro, or His"

- (ix) FEATURE:  
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 (B) LOCATION: 48  
 (D) OTHER INFORMATION: /note= "Xaa at position 48 is Leu,  
 Ser, Cys, Arg, Ile, His, Phe, Glu, Lys, Thr, Ala, Met,  
 Val, or Asn"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 49  
 (D) OTHER INFORMATION: /note= "Xaa at position 49 is Met,  
 Arg, Ala, Gly, Pro, Asn, His, or Asp"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 50  
 (D) OTHER INFORMATION: /note= "Xaa at position 50 is Glu,  
 Leu, Thr, Asp, Tyr, Lys, Asn, Ser, Ala, Ile, Val, His,  
 Phe, Met, or Gln"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 51  
 (D) OTHER INFORMATION: /note= "Xaa at position 51 is Asn,  
 Arg, Met, Pro, Ser, Thr, or His"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 52  
 (D) OTHER INFORMATION: /note= "Xaa at position 52 is Asn,  
 His, Arg, Leu, Gly, Ser, or Thr"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 53  
 (D) OTHER INFORMATION: /note= "Xaa at position 53 is  
 Leu, Thr, Ala, Gly, Glu, Pro, Lys, Ser, or Met"
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 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 54  
 (D) OTHER INFORMATION: /note= "Xaa at position 54 is Arg,  
 Asp, Ile, Ser, Val, Thr, Gln, Asn, Lys, His, Ala,  
 or Leu"
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 (B) LOCATION: 55  
 (D) OTHER INFORMATION: /note= "Xaa at position 55 is Arg,  
 Thr, Val, Ser, Leu, or Gly"
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 (B) LOCATION: 56  
 (D) OTHER INFORMATION: /note= "Xaa at position 56 is Pro,  
 Gly, Cys, Ser, Gln, Glu, Arg, His, Thr, Ala, Tyr,  
 Phe, Leu, Val, or Lys"
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 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 57  
 (D) OTHER INFORMATION: /note= "Xaa at position 57 is Asn  
 or Gly"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site

- (B) LOCATION: 58
- (D) OTHER INFORMATION: /note= "Xaa at position 58 is Leu,  
Ser, Asp, Arg, Gln, Val, or Cys"
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  - (D) OTHER INFORMATION: /note= "Xaa at position 59 is Glu,  
Tyr, His, Leu, Pro, or Arg"
- (ix) FEATURE:
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  - (D) OTHER INFORMATION: /note= "Xaa at position 60 is Ala,  
Ser, Pro, Tyr, Asn, or Thr"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 61
  - (D) OTHER INFORMATION: /note= "Xaa at position 61 is Phe,  
Asn, Glu, Pro, Lys, Arg, or Ser"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 62
  - (D) OTHER INFORMATION: /note= "Xaa at position 62 is Asn,  
His, Val, Arg, Pro, Thr, Asp, or Ile"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 63
  - (D) OTHER INFORMATION: /note= "Xaa at position 63 is Arg,  
Tyr, Trp, Lys, Ser, His, Pro, or Val"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 64
  - (D) OTHER INFORMATION: /note= "Xaa at position 64 is Ala,  
Asn, Pro, Ser, or Lys"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 65
  - (D) OTHER INFORMATION: /note= "Xaa at position 65 is Val,  
Thr, Pro, His, Leu, Phe, or Ser"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 66
  - (D) OTHER INFORMATION: /note= "Xaa at position 66 is Lys,  
Ile, Arg, Val, Asn, Glu, or Ser"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 67
  - (D) OTHER INFORMATION: /note= "Xaa at position 67 is Ser,  
Ala, Phe, Val, Gly, Asn, Ile, Pro, or His"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 68
  - (D) OTHER INFORMATION: /note= "Xaa at position 68 is Leu,  
Val, Trp, Ser, Ile, Phe, Thr, or His"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 69



- (D) OTHER INFORMATION: /note= "Xaa at position 69 is Gln, Ala, Pro, Thr, Glu, Arg, Trp, Gly, or Leu"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 70  
(D) OTHER INFORMATION: /note= "Xaa at position 70 is Asn, Leu, Val, Trp, Pro, or Ala"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 71  
(D) OTHER INFORMATION: /note= "Xaa at position 71 is Ala, Met, Leu, Pro, Arg, Glu, Thr, Gln, Trp, or Asn"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 72  
(D) OTHER INFORMATION: /note= "Xaa at position 72 is Ser, Glu, Met, Ala, His, Asn, Arg, or Asp"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 73  
(D) OTHER INFORMATION: /note= "Xaa at position 73 is Ala, Glu, Asp, Leu, Ser, Gly, Thr, or Arg"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 74  
(D) OTHER INFORMATION: /note= "Xaa at position 74 is Ile, Met, Thr, Pro, Arg, Gly, or Ala"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 75  
(D) OTHER INFORMATION: /note= "Xaa at position 75 is Glu, Lys, Gly, Asp, Pro, Trp, Arg, Ser, Gln, or Leu"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 76  
(D) OTHER INFORMATION: /note= "Xaa at position 76 is Ser, Val, Ala, Asn, Trp, Glu, Pro, Gly, or Asp"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 77  
(D) OTHER INFORMATION: /note= "Xaa at position 77 is Ile, Ser, Arg, Thr, or Leu"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 78  
(D) OTHER INFORMATION: /note= "Xaa at position 78 is Leu, Ala, Ser, Glu, Phe, Gly, or Arg"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 79  
(D) OTHER INFORMATION: /note= "Xaa at position 79 is Lys, Thr, Asn, Met, Arg, Ile, Gly, or Asp"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site

- (B) LOCATION: 80
- (D) OTHER INFORMATION: /note= "Xaa at position 80 is Asn,  
Trp, Val, Gly, Thr, Leu, Glu, or Arg"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 81
  - (D) OTHER INFORMATION: /note= "Xaa at position 81 is Leu,  
Gln, Gly, Ala, Trp, Arg, Val, or Lys"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 82
  - (D) OTHER INFORMATION: /note= "Xaa at position 82 is Leu,  
Gln, Lys, Trp, Arg, Asp, Glu, Asn, His, Thr, Ser, Ala,  
Tyr, Phe, Ile, Met, or Val"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 83
  - (D) OTHER INFORMATION: /note= "Xaa at position 83 is Pro,  
Ala, Thr, Trp, Arg, or Met"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 84
  - (D) OTHER INFORMATION: /note= "Xaa at position 84 is Cys,  
Glu, Gly, Arg, Met, or Val"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 85
  - (D) OTHER INFORMATION: /note= "Xaa at position 85 is Leu,  
Asn, Val, or Gln"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 86
  - (D) OTHER INFORMATION: /note= "Xaa at position 86 is Pro,  
Cys, Arg, Ala, or Lys"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 87
  - (D) OTHER INFORMATION: /note= "Xaa at position 87 is Leu,  
Ser, Trp, or Gly"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 88
  - (D) OTHER INFORMATION: /note= "Xaa at position 88 is Ala,  
Lys, Arg, Val, or Trp"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 89
  - (D) OTHER INFORMATION: /note= "Xaa at position 89 is Thr,  
Asp, Cys, Leu, Val, Glu, His, Asn, or Ser"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 90
  - (D) OTHER INFORMATION: /note= "Xaa at position 90 is Ala,  
Pro, Ser, Thr, Gly, Asp, Ile, or Met"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site

- (B) LOCATION: 91  
(D) OTHER INFORMATION: /note= "Xaa at position 91 is Ala,  
Pro, Ser, Thr, Phe, Leu, Asp, or His"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 92  
(D) OTHER INFORMATION: /note= "Xaa at position 92 is Pro,  
Phe, Arg, Ser, Lys, His, Ala, Gly, Ile, or Leu"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 93  
(D) OTHER INFORMATION: /note= "Xaa at position 93 is Thr,  
Asp, Ser, Asn, Pro, Ala, Leu, or Arg"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 94  
(D) OTHER INFORMATION: /note= "Xaa at position 94 is Arg,  
Ile, Ser, Glu, Leu, Val, Gln, Lys, His, Ala, or Pro"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 95  
(D) OTHER INFORMATION: /note= "Xaa at position 95 is His,  
Gln, Pro, Arg, Val, Leu, Gly, Thr, Asn, Lys, Ser, Ala,  
Trp, Phe, Ile, or Tyr"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 96  
(D) OTHER INFORMATION: /note= "Xaa at position 96 is Pro,  
Lys, Tyr, Gly, Ile, or Thr"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 97  
(D) OTHER INFORMATION: /note= "Xaa at position 97 is Ile,  
Val, Lys, Ala, or Asn"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 98  
(D) OTHER INFORMATION: /note= "Xaa at position 98 is His,  
Ile, Asn, Leu, Asp, Ala, Thr, Glu, Gln, Ser, Phe, Met,  
Val, Lys, Arg, Tyr, or Pro"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 99  
(D) OTHER INFORMATION: /note= "Xaa at position 99 is Ile,  
Leu, Arg, Asp, Val, Pro, Gln, Gly, Ser, Phe,  
or His"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 100  
(D) OTHER INFORMATION: /note= "Xaa at position 100 is  
Lys, Tyr, Leu, His, Arg, Ile, Ser, Gln, or Pro"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 101  
(D) OTHER INFORMATION: /note= "Xaa at position 101 is  
Asp, Pro, Met, Lys, His, Thr, Val, Tyr, Glu, Asn, Ser,  
Ala, Gly, Ile, Leu, or Gln"

- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 102  
 (D) OTHER INFORMATION: /note= "Xaa at position 102 is Gly,  
 Leu, Glu, Lys, Ser, Tyr, or Pro"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 103  
 (D) OTHER INFORMATION: /note= "Xaa at position 103 is Asp,  
 or Ser"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 104  
 (D) OTHER INFORMATION: /note= "Xaa at position 104 is  
 Trp, Val, Cys, Tyr, Thr, Met, Pro, Leu, Gln, Lys, Ala,  
 Phe, or Gly"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 105  
 (D) OTHER INFORMATION: /note= "Xaa at position 105 is  
 Asn, Pro, Ala, Phe, Ser, Trp, Gln, Tyr, Leu, Lys, Ile,  
 Asp, or His"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 106  
 (D) OTHER INFORMATION: /note= "Xaa at position 106 is Glu,  
 Ser, Ala, Lys, Thr, Ile, Gly, or Pro"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 108  
 (D) OTHER INFORMATION: /note= "Xaa at position 108 is Arg,  
 Lys, Asp, Leu, Thr, Ile, Gln, His, Ser, Ala, or Pro"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 109  
 (D) OTHER INFORMATION: /note= "Xaa at position 109 is Arg,  
 Thr, Pro, Glu, Tyr, Leu, Ser, or Gly"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 110  
 (D) OTHER INFORMATION: /note= "Xaa at position 110 is Lys,  
 Ala, Asn, Thr, Leu, Arg, Gln, His, Glu, Ser, Ala,  
 or Trp"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 111  
 (D) OTHER INFORMATION: /note= "Xaa at position 111 is Leu,  
 Ile, Arg, Asp, or Met"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 112  
 (D) OTHER INFORMATION: /note= "Xaa at position 112 is Thr,  
 Val, Gln, Tyr, Glu, His, Ser, or Phe"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 113

- (D) OTHER INFORMATION: /note= "Xaa at position 113 is Phe,  
Ser, Cys, His, Gly, Trp, Tyr, Asp, Lys, Leu, Ile, Val,  
or Asn"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 114  
(D) OTHER INFORMATION: /note= "Xaa at position 114 is Tyr,  
Cys, His, Ser, Trp, Arg, or Leu"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 115  
(D) OTHER INFORMATION: /note= "Xaa at position 115 is  
Leu, Asn, Val, Pro, Arg, Ala, His, Thr, Trp, or  
Met"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 116  
(D) OTHER INFORMATION: /note= "Xaa at position 116 is Lys,  
Leu, Pro, Thr, Met, Asp, Val, Glu, Arg, Trp, Ser,  
Asn, His, Ala, Tyr, Phe, Gln, or Ile"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 117  
(D) OTHER INFORMATION: /note= "Xaa at position 117 is Thr,  
Ser, Asn, Ile, Trp, Lys, or Pro"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 118  
(D) OTHER INFORMATION: /note= "Xaa at position 118 is Leu,  
Ser, Pro, Ala, Glu, Cys, Asp, or Tyr"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 119  
(D) OTHER INFORMATION: /note= "Xaa at position 119 is Glu,  
Ser, Lys, Pro, Leu, Thr, Tyr, or Arg"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 120  
(D) OTHER INFORMATION: /note= "Xaa at position 120 is Asn,  
Ala, Pro, Leu, His, Val, or Gln"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 121  
(D) OTHER INFORMATION: /note= "Xaa at position 121 is Ala,  
Ser, Ile, Asn, Pro, Lys, Asp, or Gly"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 122  
(D) OTHER INFORMATION: /note= "Xaa at position 122 is  
Gln, Ser, Met, Trp, Arg, Phe, Pro, His, Ile, Tyr,  
or Cys"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 123  
(D) OTHER INFORMATION: /note= "Xaa at position 123 is Ala,  
Met, Glu, His, Ser, Pro, Tyr, or Leu"

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

```

Ala Pro Met Thr Gln Thr Thr Ser Leu Lys Thr Ser Trp Val Asn Cys
1           5           10           15
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
20           25           30
Xaa Xaa Xaa Xaa Xaa Xaa Asn Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
35           40           45
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
50           55           60
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65           70           75           80
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
85           90           95
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Phe Xaa Xaa Xaa Xaa Xaa
100          105          110
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Gln Gln Thr Thr Leu
115          120          125

Ser Leu Ala Ile Phe
130

```

## (2) INFORMATION FOR SEQ ID NO:2:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 133 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 1
  - (D) OTHER INFORMATION: /note= "Met- may or may not precede the amino acid in position 1"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 17
  - (D) OTHER INFORMATION: /note= "Xaa at position 17 is Ser, Gly, Asp, Met, or Gln"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 18
  - (D) OTHER INFORMATION: /note= "Xaa at position 18 is Asn, His, or Ile"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 19
  - (D) OTHER INFORMATION: /note= "Xaa at position 19 is Met or Ile"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 21

- (D) OTHER INFORMATION: /note="Xaa at position 21 is Asp  
or Glu"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 23  
(D) OTHER INFORMATION: /note= "Xaa at position 23 is Ile,  
Ala, Leu, or Gly"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 24  
(D) OTHER INFORMATION: /note= "Xaa at position 24 is Ile,  
Val, or Leu"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 25  
(D) OTHER INFORMATION: /note= "Xaa at position 25 is Thr,  
His, Gln, or Ala"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 26  
(D) OTHER INFORMATION: /note= "Xaa at position 26 is His  
or Ala"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 29  
(D) OTHER INFORMATION: /note= "Xaa at position 29 is Gln,  
Asn, or Val"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 30  
(D) OTHER INFORMATION: /note= "Xaa at position 30 is Pro,  
Gly, or Gln"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 31  
(D) OTHER INFORMATION: /note= "Xaa at position 31 is Pro,  
Asp, Gly, or Gln"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 32  
(D) OTHER INFORMATION: /note= "Xaa at position 32 is Leu,  
Arg, Gln, Asn, Gly, Ala, or Glu"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 33  
(D) OTHER INFORMATION: /note= "Xaa at position 33 is Pro  
or Glu"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 34  
(D) OTHER INFORMATION: /note= "Xaa at position 34 is Leu,  
Val, Gly, Ser, Lys, Ala, Arg, Gln, Glu, Ile, Phe,  
Thr, or Met"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 35

- (D) OTHER INFORMATION: /note= "Xaa at position 35 is Leu, Ala, Asn, Pro, Gln, or Val"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 37  
(D) OTHER INFORMATION: /note= "Xaa at position 37 is Phe, Ser, Pro, or Trp"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 38  
(D) OTHER INFORMATION: /note="Xaa at position 38 is Asn or Ala"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 42  
(D) OTHER INFORMATION: /note= "Xaa at position 42 is Gly, Asp, Ser, Cys, Ala, Asn, Ile, Leu, Met, Tyr, or Arg"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 44  
(D) OTHER INFORMATION: /note="Xaa at position 44 is Asp or Glu"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 45  
(D) OTHER INFORMATION: /note= "Xaa at position 45 is Gln, Val, Met, Leu, Thr, Ala, Asn, Glu, Ser, or Lys"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 46  
(D) OTHER INFORMATION: /note= "Xaa at position 46 is Asp, Phe, Ser, Thr, Ala, Asn, Gln, Glu, His, Ile, Lys, Tyr, Val, or Cys"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 50  
(D) OTHER INFORMATION: /note= "Xaa at position 50 is Glu, Ala, Asn, Ser, or Asp"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 51  
(D) OTHER INFORMATION: /note= "Xaa at position 51 is Asn, Arg, Met, Pro, Ser, Thr, or His"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 54  
(D) OTHER INFORMATION: /note="Xaa at position 54 is Arg or Ala"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 55  
(D) OTHER INFORMATION: /note= "Xaa at position 55 is Arg, Thr, Val, Leu, or Gly"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 56



- (D) OTHER INFORMATION: /note= "Xaa at position 56 is Pro, Gly, Ser, Gln, Ala, Arg, Asn, Glu, Leu, Thr, Val, or Lys"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 60  
(D) OTHER INFORMATION: /note= "Xaa at position 60 is Ala or Ser"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 62  
(D) OTHER INFORMATION: /note= "Xaa at position 62 is Asn, Pro, Thr, or Ile"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 63  
(D) OTHER INFORMATION: /note= "Xaa at position 63 is Arg or Lys"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 64  
(D) OTHER INFORMATION: /note= "Xaa at position 64 is Ala or Asn"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 65  
(D) OTHER INFORMATION: /note= "Xaa at position 65 is Val or Thr"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 66  
(D) OTHER INFORMATION: /note= "Xaa at position 66 is Lys or Arg"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 67  
(D) OTHER INFORMATION: /note= "Xaa at position 67 is Ser Phe or His"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 68  
(D) OTHER INFORMATION: /note= "Xaa at position 68 is Leu, Ile, Phe, or His"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 69  
(D) OTHER INFORMATION: /note= "Xaa at position 69 is Gln, Ala, Pro, Thr, Glu, Arg, or Gly"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 71  
(D) OTHER INFORMATION: /note= "Xaa at position 71 is Ala, Pro, or Arg"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 72

- (D) OTHER INFORMATION: /note= "Xaa at position 72 is Ser,  
Glu, Arg, or Asp"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 73  
(D) OTHER INFORMATION: /note= "Xaa at position 73 is Ala  
or Leu"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 76  
(D) OTHER INFORMATION: /note= "Xaa at position 76 is Ser,  
Val, Ala, Asn, Glu, Pro, or Gly"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 77  
(D) OTHER INFORMATION: /note= "Xaa at position 77 is Ile  
or Leu"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 79  
(D) OTHER INFORMATION: /note= "Xaa at position 79 is  
Lys, Thr, Gly, Asn, Met, Arg, Ile, Gly, or Asp"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 80  
(D) OTHER INFORMATION: /note= "Xaa at position 80 is Asn,  
Gly, Glu, or Arg"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 82  
(D) OTHER INFORMATION: /note= "Xaa at position 82 is Leu,  
Gln, Trp, Arg, Asp, Ala, Asn, Glu, His, Ile,  
Met, Phe, Ser, Thr, Tyr, or Val"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 83  
(D) OTHER INFORMATION: /note= "Xaa at position 83 is Pro  
or Thr"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 85  
(D) OTHER INFORMATION: /note= "Xaa at position 85 is Leu  
or Val"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 87  
(D) OTHER INFORMATION: /note= "Xaa at position 87 is Leu  
or Ser"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 88  
(D) OTHER INFORMATION: /note= "Xaa at position 88 is Ala  
or Trp"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 91

- (D) OTHER INFORMATION: /note= "Xaa at position 91 is Ala or Pro"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 93  
(D) OTHER INFORMATION: /note= "Xaa at position 93 is Thr, Asp, Ser, Pro, Ala, Leu, or Arg"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 95  
(D) OTHER INFORMATION: /note= "Xaa at position 95 is His, Pro, Arg, Val, Leu, Gly, Asn, Phe, Ser, or Thr"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 96  
(D) OTHER INFORMATION: /note= "Xaa at position 96 is Pro or Tyr"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 97  
(D) OTHER INFORMATION: /note= "Xaa at position 97 is Ile or Val"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 98  
(D) OTHER INFORMATION: /note= "Xaa at position 98 is His, Ile, Asn, Leu, Ala, Thr, Arg, Gln, Lys, Met, Ser, Tyr, Val, or Pro"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 99  
(D) OTHER INFORMATION: /note= "Xaa at position 99 is Ile, Leu, or Val"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 100  
(D) OTHER INFORMATION: /note= "Xaa at position 100 is Lys, Arg, Ile, Gln, Pro, or Ser"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 101  
(D) OTHER INFORMATION: /note= "Xaa at position 101 is Asp, Pro, Met, Lys, Thr, His, Asn, Ile, Leu, or Tyr"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 104  
(D) OTHER INFORMATION: /note= "Xaa at position 104 is Trp or Leu"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 105  
(D) OTHER INFORMATION: /note= "Xaa at position 105 is Asn, Pro, Ala, Ser, Trp, Gln, Tyr, Leu, Lys, Ile, Asp, or His"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site

- (B) LOCATION: 106
- (D) OTHER INFORMATION: /note= "Xaa at position 106 is Glu or Gly"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 108
  - (D) OTHER INFORMATION: /note="Xaa at position 108 is Arg, Ala, or Ser"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 109
  - (D) OTHER INFORMATION: /note= "Xaa at position 109 is Arg, Thr, Glu, Leu, or Ser"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 112
  - (D) OTHER INFORMATION: /note= "Xaa at position 112 is Thr, Val, or Gln"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 114
  - (D) OTHER INFORMATION: /note= "Xaa at position 114 is Tyr or Trp"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 115
  - (D) OTHER INFORMATION: /note= "Xaa at position 115 is Leu or Ala"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 116
  - (D) OTHER INFORMATION: /note= "Xaa at position 116 is Lys, Thr, Val, Trp, Ser, Ala, His, Met, Phe, Tyr, or Ile"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 117
  - (D) OTHER INFORMATION: /note= "Xaa at position 117 is Thr or Ser"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 120
  - (D) OTHER INFORMATION: /note= "Xaa at position 120 is Asn, Pro, Leu, His, Val, or Gln"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 121
  - (D) OTHER INFORMATION: /note= "Xaa at position 121 is Ala, Ser, Ile, Asn, Pro, Asp, or Gly"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 122
  - (D) OTHER INFORMATION: /note= "Xaa at position 122 is Gln, Ser, Met, Trp, Arg, Phe, Pro, His, Ile, Tyr, or Cys"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site

- (B) LOCATION: 123  
 (D) OTHER INFORMATION: /note= "Xaa at position 123 is Ala,  
 Met, Glu, His, Ser, Pro, Tyr, or Leu"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```

Ala Pro Met Thr Gln Thr Thr Ser Leu Lys Thr Ser Trp Val Asn Cys
 1           5           10           15
Xaa Xaa Xaa Ile Xaa Glu Xaa Xaa Xaa Leu Lys Xaa Xaa Xaa Xaa
 20           25           30
Xaa Xaa Xaa Asp Xaa Xaa Asn Leu Asn Xaa Glu Xaa Xaa Xaa Ile Leu
 35           40           45
Met Xaa Xaa Asn Leu Xaa Xaa Xaa Asn Leu Glu Xaa Phe Xaa Xaa Xaa
 50           55           60
Xaa Xaa Xaa Xaa Xaa Asn Xaa Xaa Xaa Ile Glu Xaa Xaa Leu Xaa Xaa
 65           70           75           80
Leu Xaa Xaa Cys Xaa Pro Xaa Xaa Thr Ala Xaa Pro Xaa Arg Xaa Xaa
 85           90           95
Xaa Xaa Xaa Xaa Xaa Gly Asp Xaa Xaa Xaa Phe Xaa Xaa Lys Leu Xaa
100           105           110
Phe Xaa Xaa Xaa Xaa Leu Glu Xaa Xaa Xaa Xaa Gln Gln Thr Thr Leu
115           120           125
Ser Leu Ala Ile Phe
130

```

(2) INFORMATION FOR SEQ ID NO:3:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 133 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 1  
 (D) OTHER INFORMATION: /note= "Met- may or may not precede  
 the amino acid in position 1"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 17  
 (D) OTHER INFORMATION: /note= "Xaa at position 17 is Ser,  
 Gly, Asp, or Gln"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 18  
 (D) OTHER INFORMATION: /note= "Xaa at position 18 is Asn,  
 His, or Ile"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 23  
 (D) OTHER INFORMATION: /note= "Xaa at position 23 is Ile,

Ala, Leu, or Gly"

- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 25
  - (D) OTHER INFORMATION: /note= "Xaa at position 25 is Thr, His, or Gln"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 26
  - (D) OTHER INFORMATION: /note= "Xaa at position 26 is His or Ala"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 29
  - (D) OTHER INFORMATION: /note="Xaa at position 29 is Gln or Asn"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 30
  - (D) OTHER INFORMATION: /note= "Xaa at position 30 is Pro or Gly"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 32
  - (D) OTHER INFORMATION: /note= "Xaa at position 32 is Leu, Arg, Asn, or Ala"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 34
  - (D) OTHER INFORMATION: /note= "Xaa at position 34 is Leu, Val, Ser, Ala, Arg, Gln, Glu, Ile, Phe, Thr, or Met"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 35
  - (D) OTHER INFORMATION: /note= "Xaa at position 35 is Leu, Ala, Asn, or Pro"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 38
  - (D) OTHER INFORMATION: /note= "Xaa at position 38 is Asn or Ala"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 42
  - (D) OTHER INFORMATION: /note= "Xaa at position 42 is Gly, Asp, Ser, Ala, Asn, Ile, Leu, Met, Tyr, or Arg"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 45
  - (D) OTHER INFORMATION: /note= "Xaa at position 45 is Gln, Val, Met, Leu, Ala, Asn, Glu, or Lys"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 46
  - (D) OTHER INFORMATION: /note= "Xaa at position 46 is Asp, Phe, Ser, Gln, Glu, His, Val, or Thr"

- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 50  
 (D) OTHER INFORMATION: /note= "Xaa at position 50 is Glu,  
 Asn, Ser, or Asp"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 51  
 (D) OTHER INFORMATION: /note= "Xaa at position 51 is Asn,  
 Arg, Pro, Thr, or His"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 55  
 (D) OTHER INFORMATION: /note= "Xaa at position 55 is Arg,  
 Leu, or Gly"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 56  
 (D) OTHER INFORMATION: /note= "Xaa at position 56 is Pro,  
 Gly, Ser, Ala, Asn, Val, Leu, or Gln"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 62  
 (D) OTHER INFORMATION: /note= "Xaa at position 62 is Asn,  
 Pro, or Thr"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 64  
 (D) OTHER INFORMATION: /note= "Xaa at position 64 is Ala  
 or Asn"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 65  
 (D) OTHER INFORMATION: /note= "Xaa at position 65 is Val  
 or Thr"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 67  
 (D) OTHER INFORMATION: /note= "Xaa at position 67 is Ser  
 or Phe"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 68  
 (D) OTHER INFORMATION: /note= "Xaa at position 68 is Leu  
 or Phe"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 69  
 (D) OTHER INFORMATION: /note= "Xaa at position 69 is Gln,  
 Ala, Glu, or Arg"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 76  
 (D) OTHER INFORMATION: /note= "Xaa at position 76 is Ser,  
 Val, Asn, Pro, or Gly"

- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 77  
 (D) OTHER INFORMATION: /note= "Xaa at position 77 is Ile  
 or Leu"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 79  
 (D) OTHER INFORMATION: /note= "Xaa at position 79 is Lys,  
 Asn, Met, Arg, Ile, or Gly"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 80  
 (D) OTHER INFORMATION: /note= "Xaa at position 80 is Asn,  
 Gly, Glu, or Arg"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 82  
 (D) OTHER INFORMATION: /note= "Xaa at position 82 is Leu,  
 Gln, Trp, Arg, Asp, Asn, Glu, His, Met, Phe, Ser,  
 Thr, Tyr, or Val"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 87  
 (D) OTHER INFORMATION: /note= "Xaa at position 87 is Leu  
 or Ser"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 88  
 (D) OTHER INFORMATION: /note= "Xaa at position 88 is Ala  
 or Trp"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 91  
 (D) OTHER INFORMATION: /note= "Xaa at position 91 is Ala  
 or Pro"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 93  
 (D) OTHER INFORMATION: /note= "Xaa at position 93 is Thr,  
 Asp, or Ala"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 95  
 (D) OTHER INFORMATION: /note= "Xaa at position 95 is His,  
 Pro, Arg, Val, Gly, Asn, Ser, or Thr"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 98  
 (D) OTHER INFORMATION: /note= "Xaa at position 98 is His,  
 Ile, Asn, Ala, Thr, Gln, Glu, Lys, Met, Ser, Tyr,  
 Val, or Leu"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 99  
 (D) OTHER INFORMATION: /note= "Xaa at position 99 is Ile  
 or Leu"



- (ix) FEATURE:  
    (A) NAME/KEY: Modified-site  
    (B) LOCATION: 100  
    (D) OTHER INFORMATION: /note= "Xaa at position 100 is Lys  
        or Arg"
- (ix) FEATURE:  
    (A) NAME/KEY: Modified-site  
    (B) LOCATION: 101  
    (D) OTHER INFORMATION: /note= "Xaa at position 101 is Asp,  
        Pro, Met, Lys, Thr, His, Asn, Ile, Leu, or Tyr"
- (ix) FEATURE:  
    (A) NAME/KEY: Modified-site  
    (B) LOCATION: 105  
    (D) OTHER INFORMATION: /note= "Xaa at position 105 is Asn,  
        Pro, Ser, Ile, or Asp"
- (ix) FEATURE:  
    (A) NAME/KEY: Modified-site  
    (B) LOCATION: 108  
    (D) OTHER INFORMATION: /note= "Xaa at position 108 is Arg, Ala,  
        or Ser"
- (ix) FEATURE:  
    (A) NAME/KEY: Modified-site  
    (B) LOCATION: 109  
    (D) OTHER INFORMATION: /note= "Xaa at position 109 is Arg,  
        Thr, Glu, Leu, or Ser"
- (ix) FEATURE:  
    (A) NAME/KEY: Modified-site  
    (B) LOCATION: 112  
    (D) OTHER INFORMATION: /note= "Xaa at position 112 is Thr  
        or Gln"
- (ix) FEATURE:  
    (A) NAME/KEY: Modified-site  
    (B) LOCATION: 116  
    (D) OTHER INFORMATION: /note= "Xaa at position 116 is Lys,  
        Val, Trp, Ala, His, Phe, Tyr, or Ile"
- (ix) FEATURE:  
    (A) NAME/KEY: Modified-site  
    (B) LOCATION: 117  
    (D) OTHER INFORMATION: /note= "Xaa at position 117 is Thr  
        or Ser"
- (ix) FEATURE:  
    (A) NAME/KEY: Modified-site  
    (B) LOCATION: 120  
    (D) OTHER INFORMATION: /note= "Xaa at position 120 is Asn,  
        Pro, Leu, His, Val, or Gln"
- (ix) FEATURE:  
    (A) NAME/KEY: Modified-site  
    (B) LOCATION: 121  
    (D) OTHER INFORMATION: /note= "Xaa at position 121 is Ala,  
        Ser, Ile, Pro, or Asp"
- (ix) FEATURE:  
    (A) NAME/KEY: Modified-site  
    (B) LOCATION: 122  
    (D) OTHER INFORMATION: /note= "Xaa at position 122 is Gln,  
        Met, Trp, Phe, Pro, His, Ile, or Tyr"
- (ix) FEATURE:

- (A) NAME/KEY: Modified-site
- (B) LOCATION: 123
- (D) OTHER INFORMATION: /note= "Xaa at position 123 is Ala, Met, Glu, Ser, or Leu"

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

```

Ala Pro Met Thr Gln Thr Thr Ser Leu Lys Thr Ser Trp Val Asn Cys
 1             5             10             15
Xaa Xaa Met Ile Asp Glu Xaa Ile Xaa Xaa Leu Lys Xaa Xaa Pro Xaa
20             25             30
Pro Xaa Xaa Asp Phe Xaa Asn Leu Asn Xaa Glu Asp Xaa Xaa Ile Leu
35             40             45
Met Xaa Xaa Asn Leu Arg Xaa Xaa Asn Leu Glu Ala Phe Xaa Arg Xaa
50             55             60
Xaa Lys Xaa Xaa Xaa Asn Ala Ser Ala Ile Glu Xaa Xaa Leu Xaa Xaa
65             70             75             80
Leu Xaa Pro Cys Leu Pro Xaa Xaa Thr Ala Xaa Pro Xaa Arg Xaa Pro
85             90             95
Ile Xaa Xaa Xaa Xaa Gly Asp Trp Xaa Glu Phe Xaa Xaa Lys Leu Xaa
100            105            110
Phe Tyr Leu Xaa Xaa Leu Glu Xaa Xaa Xaa Xaa Gln Gln Thr Thr Leu
115            120            125

Ser Leu Ala Ile Phe
130

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## (2) INFORMATION FOR SEQ ID NO:4:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 111 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 1
  - (D) OTHER INFORMATION: /note= "Met- or Met-Ala- may or may not precede the amino acid in position 1"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 3
  - (D) OTHER INFORMATION: /note= "Xaa at position 3 is Ser, Lys, Gly, Asp, Met, Gln, or Arg"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 4
  - (D) OTHER INFORMATION: /note= "Xaa at position 4 is Asn, His, Leu, Ile, Phe, Arg, or Gln"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 5

- (D) OTHER INFORMATION: /note= "Xaa at position 5 is Met,  
Phe, Ile, Arg, Gly, Ala, or Cys"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 6  
(D) OTHER INFORMATION: /note= "Xaa at position 6 is Ile,  
Cys, Gln, Glu, Arg, Pro, or Ala"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 7  
(D) OTHER INFORMATION: /note= "Xaa at position 7 is Asp,  
Phe, Lys, Arg, Ala, Gly, Glu, Gln, Asn, Thr, Ser,  
or Val"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 8  
(D) OTHER INFORMATION: /note= "Xaa at position 8 is Glu,  
Trp, Pro, Ser, Ala, His, Asp, Asn, Gln, Leu, Val,  
or Gly"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 9  
(D) OTHER INFORMATION: /note= "Xaa at position 9 is  
Ile, Val, Ala, Leu, Gly, Trp, Lys, Phe, Leu, Ser  
or Arg"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 10  
(D) OTHER INFORMATION: /note= "Xaa at position 10 is Ile,  
Gly, Val, Arg, Ser, Phe, or Leu"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 11  
(D) OTHER INFORMATION: /note= "Xaa at position 11 is Thr,  
His, Gly, Gln, Arg, Pro, or Ala"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 12  
(D) OTHER INFORMATION: /note= "Xaa at position 12 is His,  
Thr, Phe, Gly, Arg, Ala, or Trp"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 13  
(D) OTHER INFORMATION: /note= "Xaa at position 13 is Leu,  
Gly, Arg, Thr, Ser, or Ala"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 14  
(D) OTHER INFORMATION: /note= "Xaa at position 14 is Lys,  
Arg, Leu, Gln, Gly, Pro, Val, or Trp"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 15  
(D) OTHER INFORMATION: /note= "Xaa at position 15 is Gln,  
Asn, Leu, Pro, Arg, or Val"
- (ix) FEATURE:

- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 16
  - (D) OTHER INFORMATION: /note= "Xaa at position 16 is Pro, His, Thr, Gly, Asp, Gln, Ser, Leu, or Lys"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 17
  - (D) OTHER INFORMATION: /note= "Xaa at position 17 is Pro, Asp, Gly, Ala, Arg, Leu, or Gln"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 18
  - (D) OTHER INFORMATION: /note= "Xaa at position 18 is Leu, Val, Arg, Gln, Asn, Gly, Ala, or Glu"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 19
  - (D) OTHER INFORMATION: /note= "Xaa at position 19 is Pro, Leu, Gln, Ala, Thr, or Glu"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 20
  - (D) OTHER INFORMATION: /note= "Xaa at position 20 is Leu, Val, Gly, Ser, Lys, Glu, Gln, Thr, Arg, Ala, Phe, Ile, or Met"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 21
  - (D) OTHER INFORMATION: /note= "Xaa at position 21 is Leu, Ala, Gly, Asn, Pro, Gln, or Val"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 22
  - (D) OTHER INFORMATION: /note= "Xaa at position 22 is Asp, Leu, or Val"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 23
  - (D) OTHER INFORMATION: /note= "Xaa at position 23 is Phe, Ser, Pro, Trp, or Ile"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 24
  - (D) OTHER INFORMATION: /note= "Xaa at position 24 is Asn or Ala"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 26
  - (D) OTHER INFORMATION: /note= "Xaa at position 26 is Leu, Trp, or Arg"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 27
  - (D) OTHER INFORMATION: /note= "Xaa at position 27 is Asn, Cys, Arg, Leu, His, Met, or Pro"
- (ix) FEATURE:

- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 28
  - (D) OTHER INFORMATION: /note= "Xaa at position 28 is Gly, Asp, Ser, Cys, Ala, Lys, Asn, Thr, Leu, Val, Glu, Phe, Tyr, Ile, or Met"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 29
  - (D) OTHER INFORMATION: /note= "Xaa at position 29 is Glu, Asn, Tyr, Leu, Phe, Asp, Ala, Cys, Gln, Arg, Thr, Gly, or Ser"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 30
  - (D) OTHER INFORMATION: /note= "Xaa at position 30 is Asp, Ser, Leu, Arg, Lys, Thr, Met, Trp, Glu, Asn, Gln, Ala, or Pro"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 31
  - (D) OTHER INFORMATION: /note= "Xaa at position 31 is Gln, Pro, Phe, Val, Met, Leu, Thr, Lys, Asp, Asn, Arg, Ser, Ala, Ile, Glu, His, or Trp"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 32
  - (D) OTHER INFORMATION: /note= "Xaa at position 32 is Asp, Phe, Ser, Thr, Cys, Glu, Asn, Gln, Lys, His, Ala, Tyr, Ile, Val, or Gly"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 33
  - (D) OTHER INFORMATION: /note= "Xaa at position 33 is Ile, Gly, Val, Ser, Arg, Pro, or His"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 34
  - (D) OTHER INFORMATION: /note= "Xaa at position 34 is Leu, Ser, Cys, Arg, Ile, His, Phe, Glu, Lys, Thr, Ala, Met, Val, or Asn"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 35
  - (D) OTHER INFORMATION: /note= "Xaa at position 35 is Met, Arg, Ala, Gly, Pro, Asn, His, or Asp"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 36
  - (D) OTHER INFORMATION: /note= "Xaa at position 36 is Glu, Leu, Thr, Asp, Tyr, Lys, Asn, Ser, Ala, Ile, Val, His, Phe, Met, or Gln"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 37
  - (D) OTHER INFORMATION: /note= "Xaa at position 37 is Asn, Arg, Met, Pro, Ser, Thr, or His"
- (ix) FEATURE:

- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 38
  - (D) OTHER INFORMATION: /note= "Xaa at position 38 is Asn,  
His, Arg, Leu, Gly, Ser, or Thr"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 39
  - (D) OTHER INFORMATION: /note= "Xaa at position 39 is  
Leu, Thr, Ala, Gly, Glu, Pro, Lys, Ser, or Met"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 40
  - (D) OTHER INFORMATION: /note= "Xaa at position 40 is Arg,  
Asp, Ile, Ser, Val, Thr, Gln, Asn, Lys, His,  
Ala, or Leu"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 41
  - (D) OTHER INFORMATION: /note= "Xaa at position 41 is Arg,  
Thr, Val, Ser, Leu, or Gly"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 42
  - (D) OTHER INFORMATION: /note= "Xaa at position 42 is Pro,  
Gly, Cys, Ser, Gln, Glu, Arg, His, Thr, Ala, Tyr,  
Phe, Leu, Val, or Lys"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 43
  - (D) OTHER INFORMATION: /note= "Xaa at position 43 is Asn  
or Gly"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 44
  - (D) OTHER INFORMATION: /note= "Xaa at position 44 is Leu,  
Ser, Asp, Arg, Gln, Val, or Cys"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 45
  - (D) OTHER INFORMATION: /note= "Xaa at position 45 is Glu,  
Tyr, His, Leu, Pro, or Arg"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 46
  - (D) OTHER INFORMATION: /note= "Xaa at position 46 is Ala,  
Ser, Pro, Tyr, Asn, or Thr"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 47
  - (D) OTHER INFORMATION: /note= "Xaa at position 47 is Phe,  
Asn, Glu, Pro, Lys, Arg, or Ser"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 48
  - (D) OTHER INFORMATION: /note= "Xaa at position 48 is Asn,  
His, Val, Arg, Pro, Thr, Asp, or Ile"

- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 49  
 (D) OTHER INFORMATION: /note= "Xaa at position 49 is Arg,  
 Tyr, Trp, Lys, Ser, His, Pro, or Val"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 50  
 (D) OTHER INFORMATION: /note= "Xaa at position 50 is Ala,  
 Asn, Pro, Ser, or Lys"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 51  
 (D) OTHER INFORMATION: /note= "Xaa at position 51 is Val,  
 Thr, Pro, His, Leu, Phe, or Ser"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 52  
 (D) OTHER INFORMATION: /note= "Xaa at position 52 is Lys,  
 Ile, Arg, Val, Asn, Glu, or Ser"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 53  
 (D) OTHER INFORMATION: /note= "Xaa at position 53 is Ser,  
 Ala, Phe, Val, Gly, Asn, Ile, Pro, or His"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 54  
 (D) OTHER INFORMATION: /note= "Xaa at position 54 is Leu,  
 Val, Trp, Ser, Ile, Phe, Thr, or His"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 55  
 (D) OTHER INFORMATION: /note= "Xaa at position 55 is Gln,  
 Ala, Pro, Thr, Glu, Arg, Gly, or Leu"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 56  
 (D) OTHER INFORMATION: /note= "Xaa at position 56 is Asn,  
 Leu, Val, Trp, Pro, or Ala"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 57  
 (D) OTHER INFORMATION: /note= "Xaa at position 57 is Ala,  
 Met, Leu, Pro, Arg, Glu, Thr, Gln, Trp, or Asn"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 58  
 (D) OTHER INFORMATION: /note= "Xaa at position 58 is Ser,  
 Glu, Met, Ala, His, Asn, Arg, or Asp"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 59  
 (D) OTHER INFORMATION: /note= "Xaa at position 59 is Ala,  
 Glu, Asp, Leu, Ser, Gly, Thr, or Arg"
- (ix) FEATURE:

- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 60
  - (D) OTHER INFORMATION: /note= "Xaa at position 60 is Ile,  
Met, Thr, Pro, Arg, Gly, Ala"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 61
  - (D) OTHER INFORMATION: /note= "Xaa at position 61 is  
Glu, Lys, Gly, Asp, Pro, Trp, Arg, Ser, Gln,  
or Leu"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 62
  - (D) OTHER INFORMATION: /note= "Xaa at position 62 is Ser,  
Val, Ala, Asn, Trp, Glu, Pro, Gly, or Asp"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 63
  - (D) OTHER INFORMATION: /note= "Xaa at position 63 is Ile,  
Ser, Arg, Thr, or Leu"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 64
  - (D) OTHER INFORMATION: /note= "Xaa at position 64 is Leu,  
Ala, Ser, Glu, Phe, Gly, or Arg"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 65
  - (D) OTHER INFORMATION: /note= "Xaa at position 65 is Lys,  
Thr, Gly, Asn, Met, Arg, Ile, or Asp"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 66
  - (D) OTHER INFORMATION: /note= "Xaa at position 66 is Asn,  
Trp, Val, Gly, Thr, Leu, Glu, or Arg"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 67
  - (D) OTHER INFORMATION: /note= "Xaa at position 67 is Leu,  
Gln, Gly, Ala, Trp, Arg, Val, or Lys"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 68
  - (D) OTHER INFORMATION: /note= "Xaa at position 68 is Leu,  
Gln, Lys, Trp, Arg, Asp, Glu, Asn, His, Thr, Ser, Ala,  
Tyr, Phe, Ile, Met, or Val"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 69
  - (D) OTHER INFORMATION: /note= "Xaa at position 69 is Pro,  
Ala, Thr, Trp, Arg, or Met"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 70
  - (D) OTHER INFORMATION: /note= "Xaa at position 70 is Cys,  
Glu, Gly, Arg, Met, or Val"



- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 71
  - (D) OTHER INFORMATION: /note= "Xaa at position 71 is Leu, Asn, Val, or Gln"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 72
  - (D) OTHER INFORMATION: /note= "Xaa at position 72 is Pro, Cys, Arg, Ala, or Lys"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 73
  - (D) OTHER INFORMATION: /note= "Xaa at position 73 is Leu, Ser, Trp, or Gly"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 74
  - (D) OTHER INFORMATION: /note= "Xaa at position 74 is Ala, Lys, Arg, Val, or Trp"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 75
  - (D) OTHER INFORMATION: /note= "Xaa at position 75 is Thr, Asp, Cys, Leu, Val, Glu, His, Asn, or Ser"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 76
  - (D) OTHER INFORMATION: /note= "Xaa at position 76 is Ala, Pro, Ser, Thr, Gly, Asp, Ile, or Met"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 77
  - (D) OTHER INFORMATION: /note= "Xaa at position 77 is Ala, Pro, Ser, Thr, Phe, Leu, Asp, or His"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 78
  - (D) OTHER INFORMATION: /note= "Xaa at position 78 is Pro, Phe, Arg, Ser, Lys, His, Ala, Gly, Ile, or Leu"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 79
  - (D) OTHER INFORMATION: /note= "Xaa at position 79 is Thr, Asp, Ser, Asn, Pro, Ala, Leu, or Arg"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 80
  - (D) OTHER INFORMATION: /note= "Xaa at position 80 is Arg, Ile, Ser, Glu, Leu, Val, Gln, Lys, His, Ala, or Pro"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 81
  - (D) OTHER INFORMATION: /note= "Xaa at position 81 is His, Gln, Pro, Arg, Val, Leu, Gly, Thr, Asn, Lys, Ser, Ala, Trp, Phe, Ile, or Tyr"

- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 82  
 (D) OTHER INFORMATION: /note= "Xaa at position 82 is Pro,  
 Lys, Tyr, Gly, Ile, or Thr"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 83  
 (D) OTHER INFORMATION: /note= "Xaa at position 83 is Ile,  
 Val, Lys, Ala, or Asn"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 84  
 (D) OTHER INFORMATION: /note= "Xaa at position 84 is His,  
 Ile, Asn, Leu, Asp, Ala, Thr, Glu, Gln, Ser,  
 Phe, Met, Val, Lys, Arg, Tyr, or Pro"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 85  
 (D) OTHER INFORMATION: /note= "Xaa at position 85 is  
 Ile, Leu, Arg, Asp, Val, Pro, Gln, Gly, Ser,  
 Phe, or His"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 86  
 (D) OTHER INFORMATION: /note= "Xaa at position 86 is  
 Lys, Tyr, Leu, His, Arg, Ile, Ser, Gln, or Pro"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 87  
 (D) OTHER INFORMATION: /note= "Xaa at position 87 is  
 Asp, Pro, Met, Lys, His, Thr, Val, Tyr, Glu, Asn,  
 Ser, Ala, Gly, Ile, Leu, or Gln"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 88  
 (D) OTHER INFORMATION: /note= "Xaa at position 88 Gly,  
 Leu, Glu, Lys, Ser, Tyr, or Pro"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 89  
 (D) OTHER INFORMATION: /note= "Xaa at position 89 is Asp  
 or Ser"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 90  
 (D) OTHER INFORMATION: /note= "Xaa at position 90 is  
 Trp, Val, Cys, Tyr, Thr, Met, Pro, Leu, Gln, Lys,  
 Ala, Phe, or Gly"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 91  
 (D) OTHER INFORMATION: /note= "Xaa at position 91 is  
 Asn, Pro, Ala, Phe, Ser, Trp, Gln, Tyr, Leu, Lys,  
 Ile, Asp, or His"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site

- (B) LOCATION: 92
  - (D) OTHER INFORMATION: /note= "Xaa at position 92 is Glu, Ser, Ala, Lys, Thr, Ile, Gly, or Pro"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 94
  - (D) OTHER INFORMATION: /note= "Xaa at position 94 is Arg, Lys, Asp, Leu, Thr, Ile, Gln, His, Ser, Ala, or Pro"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 95
  - (D) OTHER INFORMATION: /note= "Xaa at position 95 is Arg, Thr, Pro, Glu, Tyr, Leu, Ser, or Gly"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 96
  - (D) OTHER INFORMATION: /note= "Xaa at position 96 is Lys, Asn, Thr, Leu, Gln, Arg, His, Glu, Ser, Ala, or Trp"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 97
  - (D) OTHER INFORMATION: /note= "Xaa at position 97 is Leu, Ile, Arg, Asp, or Met"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 98
  - (D) OTHER INFORMATION: /note= "Xaa at position 98 is Thr, Val, Gln, Tyr, Glu, His, Ser, or Phe"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 99
  - (D) OTHER INFORMATION: /note= "Xaa at position 99 is Phe, Ser, Cys, His, Gly, Trp, Tyr, Asp, Lys, Leu, Ile, Val, or Asn"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 100
  - (D) OTHER INFORMATION: /note= "Xaa at position 100 is Tyr, Cys, His, Ser, Trp, Arg, or Leu"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 101
  - (D) OTHER INFORMATION: /note= "Xaa at position 101 is Leu, Asn, Val, Pro, Arg, Ala, His, Thr, Trp, or Met"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 102
  - (D) OTHER INFORMATION: /note= "Xaa at position 102 is Lys, Leu, Pro, Thr, Met, Asp, Val, Glu, Arg, Trp, Ser, Asn, His, Ala, Tyr, Phe, Gln, or Ile"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 103
  - (D) OTHER INFORMATION: /note= "Xaa at position 103 is Thr, Ser, Asn, Ile, Trp, Lys, or Pro"

(ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 104  
 (D) OTHER INFORMATION: /note= "Xaa at position 104 is Leu,  
 Ser, Pro, Ala, Glu, Cys, Asp, or Tyr"

(ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 105  
 (D) OTHER INFORMATION: /note= "Xaa at position 105 is Glu,  
 Ser, Lys, Pro, Leu, Thr, Tyr, or Arg"

(ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 106  
 (D) OTHER INFORMATION: /note= "Xaa at position 106 is Asn,  
 Ala, Pro, Leu, His, Val or Gln"

(ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 107  
 (D) OTHER INFORMATION: /note= "Xaa at position 107 is Ala,  
 Ser, Ile, Asn, Pro, Lys, Asp, or Gly"

(ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 108  
 (D) OTHER INFORMATION: /note= "Xaa at position 108 is  
 Gln, Ser, Met, Trp, Arg, Phe, Pro, His, Ile, Tyr,  
 or Cys"

(ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 109  
 (D) OTHER INFORMATION: /note= "Xaa at position 109 is Ala,  
 Met, Glu, His, Ser, Pro, Tyr, or Leu"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Asn	Cys	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
1				5						10						15	
Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Asn	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
				20				25								30	
Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
				35				40							45		
Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
				50				55							60		
Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
				65				70							75		80
Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
				85				90									95
Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Gln	Gln
				100				105								110	

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 111 amino acids  
 (B) TYPE: amino acid

- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 1  
 (D) OTHER INFORMATION: /note= "Met- or Met-Ala- may or may  
 not precede the amino acid in position 1"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 3  
 (D) OTHER INFORMATION: /note= "Xaa at position 3 is Ser,  
 Gly, Asp, Met, or Gln"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 4  
 (D) OTHER INFORMATION: /note= "Xaa at position 4 is Asn,  
 His, or Ile"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 5  
 (D) OTHER INFORMATION: /note= "Xaa at position 5 is Met  
 or Ile"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 7  
 (C) OTHER INFORMATION: /note= "Xaa at position 7 is Asp or Glu"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 9  
 (D) OTHER INFORMATION: /note= "Xaa at position 9 is Ile,  
 Ala, Leu, or Gly"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 10  
 (D) OTHER INFORMATION: /note= "Xaa at position 10 is Ile,  
 Val, or Leu"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 11  
 (D) OTHER INFORMATION: /note= "Xaa at position 11 is Thr,  
 His, Gln, or Ala"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 12  
 (D) OTHER INFORMATION: /note= "Xaa at position 12 is His  
 or Ala"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 15  
 (D) OTHER INFORMATION: /note= "Xaa at position 15 is Gln,  
 Asn, or Val"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 16

- (D) OTHER INFORMATION: /note= "Xaa at position 16 is Pro, Gly, or Gln"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 17  
(D) OTHER INFORMATION: /note= "Xaa at position 17 is Pro, Asp, Gly, or Gln"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 18  
(D) OTHER INFORMATION: /note= "Xaa at position 18 is Leu, Arg, Gln, Asn, Gly, Ala, or Glu"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 19  
(D) OTHER INFORMATION: /note= "Xaa at position 19 is Pro or Glu"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 20  
(D) OTHER INFORMATION: /note= "Xaa at position 20 is Leu, Val, Gly, Ser, Lys, Ala, Arg, Gln, Glu, Ile, Phe, Thr, or Met"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 21  
(D) OTHER INFORMATION: /note= "Xaa at position 21 is Leu, Ala, Asn, Pro, Gln, or Val"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 23  
(D) OTHER INFORMATION: /note= "Xaa at position 23 is Phe, Ser, Pro, or Trp"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 24  
(D) OTHER INFORMATION: /note= "Xaa at position 24 is Asn or Ala"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 28  
(D) OTHER INFORMATION: /note= "Xaa at position 28 is Gly, Asp, Ser, Cys, Ala, Asn, Ile, Leu, Met, Tyr, or Arg"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 30  
(D) OTHER INFORMATION: /note= "Xaa at position 30 is Asp or Glu"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 31  
(D) OTHER INFORMATION: /note= "Xaa at position 31 is Gln, Val, Met, Leu, Thr, Ala, Asn, Glu, Ser, or Lys"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 32

- (D) OTHER INFORMATION: /note= "Xaa at position 32 is Asp,  
Phe, Ser, Thr, Ala, Asn, Gln, Glu, His, Ile, Lys,  
Tyr, Val, or Cys"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 36  
(D) OTHER INFORMATION: /note= "Xaa at position 36 is Glu,  
Ala, Asn, Ser, or Asp"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 37  
(D) OTHER INFORMATION: /note= "Xaa at position 37 is Asn,  
Arg, Met, Pro, Ser, Thr, or His"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 40  
(D) OTHER INFORMATION: /note= "Xaa at position 40 is Arg  
or Ala"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 41  
(D) OTHER INFORMATION: /note= "Xaa at position 41 is Arg,  
Thr, Val, Leu, or Gly"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 42  
(D) OTHER INFORMATION: /note= "Xaa at position 42 is Pro,  
Gly, Ser, Gln, Ala, Arg, Asn, Glu, Leu, Thr, Val,  
or Lys"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 46  
(D) OTHER INFORMATION: /note= "Xaa at position 46 is Ala  
or Ser"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 48  
(D) OTHER INFORMATION: /note= "Xaa at position 48 is Asn,  
Pro, Thr, or Ile"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 49  
(D) OTHER INFORMATION: /note= "Xaa at position 49 is Arg  
or Lys"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 50  
(D) OTHER INFORMATION: /note= "Xaa at position 50 is Ala  
or Asn"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 51  
(D) OTHER INFORMATION: /note= "Xaa at position 51 is Val  
or Thr"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site

- (B) LOCATION: 52
- (D) OTHER INFORMATION: /note= "Xaa at position 52 is Lys  
or Arg"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 53
  - (D) OTHER INFORMATION: /note= "Xaa at position 53 is Ser,  
Phe, or His"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 54
  - (D) OTHER INFORMATION: /note= "Xaa at position 54 is Leu,  
Ile, Phe, or His"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 55
  - (D) OTHER INFORMATION: /note= "Xaa at position 55 is Gln,  
Ala, Pro, Thr, Glu, Arg, or Gly"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 57
  - (D) OTHER INFORMATION: /note= "Xaa at position 57 is Ala,  
Pro, or Arg"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 58
  - (D) OTHER INFORMATION: /note= "Xaa at position 58 is Ser,  
Glu, Arg, or Asp"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 59
  - (D) OTHER INFORMATION: /note= "Xaa at position 59 is Ala  
or Leu"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 62
  - (D) OTHER INFORMATION: /note= "Xaa at position 62 is Ser,  
Val, Ala, Asn, Glu, Pro, or Gly"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 63
  - (D) OTHER INFORMATION: /note= "Xaa at position 63 is Ile  
or Leu"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 65
  - (D) OTHER INFORMATION: /note= "Xaa at position 65 is Lys,  
Thr, Gly, Asn, Met, Arg, Ile, Gly, or Asp"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 66
  - (D) OTHER INFORMATION: /note= "Xaa at position 66 is Asn,  
Gly, Glu, or Arg"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 68



- (D) OTHER INFORMATION: /note= "Xaa at position 68 is Leu,  
Gln, Trp, Arg, Asp, Ala, Asn, Glu, His, Ile, Met,  
Phe, Ser, Thr, Tyr, or Val"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 69  
(D) OTHER INFORMATION: /note= "Xaa at position 69 is Pro  
or Thr"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 71  
(D) OTHER INFORMATION: /note= "Xaa at position 71 is Leu  
or Val"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 73  
(D) OTHER INFORMATION: /note= "Xaa at position 73 is Leu  
or Ser"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 74  
(D) OTHER INFORMATION: /note= "Xaa at position 74 is Ala  
or Trp"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 77  
(D) OTHER INFORMATION: /note= "Xaa at position 77 is Ala  
or Pro"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 79  
(D) OTHER INFORMATION: /note= "Xaa at position 79 is Thr,  
Asp, Ser, Pro, Ala, Leu, or Arg"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 81  
(D) OTHER INFORMATION: /note= "Xaa at position 81 is His,  
Pro, Arg, Val, Leu, Gly, Asn, Phe, Ser, or Thr"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 82  
(D) OTHER INFORMATION: /note= "Xaa at position 82 is Pro  
or Tyr"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 83  
(D) OTHER INFORMATION: /note= "Xaa at position 83 is Ile  
or Val"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 84  
(D) OTHER INFORMATION: /note= "Xaa at position 84 is His,  
Ile, Asn, Leu, Ala, Thr, Arg, Gln, Lys,  
Met, Ser, Tyr, Val, or Pro"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site

- (B) LOCATION: 85
- (D) OTHER INFORMATION: /note= "Xaa at position 85 is Ile, Leu, or Val"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 86
  - (D) OTHER INFORMATION: /note= "Xaa at position 86 is Lys, Arg, Ile, Gln, Pro, or Ser"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 87
  - (D) OTHER INFORMATION: /note= "Xaa at position 87 is Asp, Pro, Met, Lys, His, Thr, Asn, Ile, Leu, or Tyr"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 90
  - (D) OTHER INFORMATION: /note= "Xaa at position 90 is Trp or Leu"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 91
  - (D) OTHER INFORMATION: /note= "Xaa at position 91 is Asn, Pro, Ala, Ser, Trp, Gln, Tyr, Leu, Lys, Ile, Asp, or His"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 92
  - (D) OTHER INFORMATION: /note= "Xaa at position 92 is Glu or Gly"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 94
  - (C) OTHER INFORMATION: /note= "Xaa at position 94 is Arg, Ala, or Ser"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 95
  - (D) OTHER INFORMATION: /note= "Xaa at position 95 is Arg, Thr, Glu, Leu, or Ser"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 98
  - (D) OTHER INFORMATION: /note= "Xaa at position 98 is Thr, Val, or Gln"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 100
  - (D) OTHER INFORMATION: /note= "Xaa at position 100 is Tyr or Trp"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 101
  - (D) OTHER INFORMATION: /note= "Xaa at position 101 is Leu or Ala"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 102

(D) OTHER INFORMATION: /note= "Xaa at position 102 is Lys, Thr, Val, Trp, Ser, Ala, His, Met, Phe, Tyr, or Ile"

(ix) FEATURE:

(A) NAME/KEY: Modified-site

(B) LOCATION: 103

(D) OTHER INFORMATION: /note= "Xaa at position 103 is Thr or Ser"

(ix) FEATURE:

(A) NAME/KEY: Modified-site

(B) LOCATION: 106

(D) OTHER INFORMATION: /note= "Xaa at position 106 is Asn, Pro, Leu, His, Val, or Gln"

(ix) FEATURE:

(A) NAME/KEY: Modified-site

(B) LOCATION: 107

(D) OTHER INFORMATION: /note= "Xaa at position 107 is Ala, Ser, Ile, Asn, Pro, Asp, or Gly"

(ix) FEATURE:

(A) NAME/KEY: Modified-site

(B) LOCATION: 108

(D) OTHER INFORMATION: /note= "Xaa at position 108 is Gln, Ser, Met, Trp, Arg, Phe, Pro, His, Ile, Tyr, or Cys"

(ix) FEATURE:

(A) NAME/KEY: Modified-site

(B) LOCATION: 109

(D) OTHER INFORMATION: /note= "Xaa at position 109 is Ala, Met, Glu, His, Ser, Pro, Tyr, or Leu"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Asn	Cys	Xaa	Xaa	Xaa	Ile	Xaa	Glu	Xaa	Xaa	Xaa	Leu	Lys	Xaa	Xaa
1				5				10					15	
Xaa	Xaa	Xaa	Xaa	Xaa	Asp	Xaa	Xaa	Asn	Leu	Asn	Xaa	Glu	Xaa	Xaa
			20					25				30		
Ile	Leu	Met	Xaa	Xaa	Asn	Leu	Xaa	Xaa	Xaa	Asn	Leu	Glu	Xaa	Phe
		35				40						45		
Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Asn	Xaa	Xaa	Xaa	Ile	Glu	Xaa	Leu
		50				55				60				
Xaa	Xaa	Leu	Xaa	Xaa	Cys	Xaa	Pro	Xaa	Xaa	Thr	Ala	Xaa	Pro	Xaa
65					70					75			80	
Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Gly	Asp	Xaa	Xaa	Xaa	Phe	Xaa	Lys
			85					90				95		
Leu	Xaa	Phe	Xaa	Xaa	Xaa	Xaa	Leu	Glu	Xaa	Xaa	Xaa	Gln	Gln	
			100				105					110		

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 111 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 1  
 (D) OTHER INFORMATION: /note= "Met- or Met-Ala- may or may  
 not precede the amino acid in position 1"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 3  
 (D) OTHER INFORMATION: /note= "Xaa at position 3 is Ser,  
 Gly, Asp, or Gln"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 4  
 (D) OTHER INFORMATION: /note= "Xaa at position 4 is Asn,  
 His, or Ile"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 9  
 (D) OTHER INFORMATION: /note= "Xaa at position 9 is Ile,  
 Ala, Leu, or Gly"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 11  
 (D) OTHER INFORMATION: /note= "Xaa at position 11 is Thr,  
 His, or Gln"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 12  
 (D) OTHER INFORMATION: /note= "Xaa at position 12 is His  
 or Ala"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 15  
 (D) OTHER INFORMATION: /note= "Xaa at position 15 is Gln  
 or Asn"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 16  
 (D) OTHER INFORMATION: /note= "Xaa at position 16 is Pro  
 or Gly"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 18  
 (D) OTHER INFORMATION: /note= "Xaa at position 18 is Leu,  
 Arg, Asn, or Ala"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 20  
 (D) OTHER INFORMATION: /note= "Xaa at position 20 is Leu,  
 Val, Ser, Ala, Arg, Gln, Glu, Ile, Phe, Thr, or Met"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 21  
 (D) OTHER INFORMATION: /note= "Xaa at position 21 is Leu,  
 Ala, Asn, or Pro"
- (ix) FEATURE:

- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 24
  - (D) OTHER INFORMATION: /note= "Xaa at position 24 is Asn or Ala"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 28
  - (D) OTHER INFORMATION: /note= "Xaa at position 28 is Gly, Asp, Ser, Ala, Asn, Ile, Leu, Met, Tyr, or Arg"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 31
  - (D) OTHER INFORMATION: /note= "Xaa at position 31 is Gln, Val, Met, Leu, Ala, Asn, Glu, or Lys"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 32
  - (D) OTHER INFORMATION: /note= "Xaa at position 32 is Asp, Phe, Ser, Ala, Gln, Glu, His, Val, or Thr"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 36
  - (D) OTHER INFORMATION: /note= "Xaa at position 36 is Glu, Asn, Ser, or Asp"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 37
  - (D) OTHER INFORMATION: /note= "Xaa at position 37 is Asn, Arg, Pro, Thr, or His"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 41
  - (D) OTHER INFORMATION: /note= "Xaa at position 41 is Arg, Leu, or Gly"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 42
  - (D) OTHER INFORMATION: /note= "Xaa at position 42 is Pro, Gly, Ser, Ala, Asn, Val, Leu, or Gln"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 48
  - (D) OTHER INFORMATION: /note= "Xaa at position 48 is Asn, Pro, or Thr"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 50
  - (D) OTHER INFORMATION: /note= "Xaa at position 50 is Ala or Asn"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site
  - (B) LOCATION: 51
  - (D) OTHER INFORMATION: /note= "Xaa at position 51 is Val or Thr"
- (ix) FEATURE:
- (A) NAME/KEY: Modified-site

- (B) LOCATION: 53
- (D) OTHER INFORMATION: /note= "Xaa at position 53 is Ser  
or Phe"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 54
  - (D) OTHER INFORMATION: /note= "Xaa at position 54 is Leu  
or Phe"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 55
  - (D) OTHER INFORMATION: /note= "Xaa at position 55 is Gln,  
Ala, Glu, or Arg"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 62
  - (D) OTHER INFORMATION: /note= "Xaa at position 62 is Ser,  
Val, Asn, Pro, or Gly"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 63
  - (D) OTHER INFORMATION: /note= "Xaa at position 63 is Ile  
or Leu"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 65
  - (D) OTHER INFORMATION: /note= "Xaa at position 65 is Lys,  
Asn, Met, Arg, Ile, or Gly"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 66
  - (D) OTHER INFORMATION: /note= "Xaa at position 66 is Asn,  
Gly, Glu, or Arg"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 68
  - (D) OTHER INFORMATION: /note= "Xaa at position 68 is Leu,  
Gln, Trp, Arg, Asp, Asn, Glu, His, Met, Phe, Ser,  
Thr, Tyr, or Val"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 73
  - (D) OTHER INFORMATION: /note= "Xaa at position 73 is Leu  
or Ser"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 74
  - (D) OTHER INFORMATION: /note= "Xaa at position 74 is Ala  
or Trp"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 77
  - (D) OTHER INFORMATION: /note= "Xaa at position 77 is Ala  
or Pro"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site

- (B) LOCATION: 79
- (D) OTHER INFORMATION: /note= "Xaa at position 79 is Thr, Asp, or Ala"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 81
  - (D) OTHER INFORMATION: /note= "Xaa at position 81 is His, Pro, Arg, Val, Gly, Asn, Ser, or Thr"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 84
  - (D) OTHER INFORMATION: /note= "Xaa at position 84 is His, Ile, Asn, Leu, Ala, Thr, Arg, Gln, Glu, Lys, Met, Ser, Tyr, Val, or Leu"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 85
  - (D) OTHER INFORMATION: /note= "Xaa at position 85 is Ile or Leu"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 86
  - (D) OTHER INFORMATION: /note= "Xaa at position 86 is Lys or Arg"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 87
  - (D) OTHER INFORMATION: /note= "Xaa at position 87 is Asp, Pro, Met, Lys, His, Pro, Asn, Ile, Leu, or Tyr"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 91
  - (D) OTHER INFORMATION: /note= "Xaa at position 91 is Asn, Pro, Ser, Ile, or Asp"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 94
  - (D) OTHER INFORMATION: /note= "Xaa at position 94 is Arg, Ala, or Ser"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 95
  - (D) OTHER INFORMATION: /note= "Xaa at position 95 is Arg, Thr, Glu, Leu, or Ser"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 98
  - (D) OTHER INFORMATION: /note= "Xaa at position 98 is Thr or Gln"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 102
  - (D) OTHER INFORMATION: /note= "Xaa at position 102 is Lys, Val, Trp, or Ile"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site

(B) LOCATION: 103  
 (D) OTHER INFORMATION: /note= "Xaa at position 103 is Thr,  
 Ala, His, Phe, Tyr, or Ser"

(ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 106  
 (D) OTHER INFORMATION: /note= "Xaa at position 106 is Asn,  
 Pro, Leu, His, Val, or Gln"

(ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 107  
 (D) OTHER INFORMATION: /note= "Xaa at position 107 is Ala,  
 Ser, Ile, Pro, or Asp"

(ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 108  
 (D) OTHER INFORMATION: /note= "Xaa at position 108 is Gln,  
 Met, Trp, Phe, Pro, His, Ile, or Tyr"

(ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 109  
 (D) OTHER INFORMATION: /note= "Xaa at position 109 is Ala,  
 Met, Glu, Ser, or Leu"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Asn	Cys	Xaa	Xaa	Met	Ile	Asp	Glu	Xaa	Ile	Xaa	Xaa	Leu	Lys	Xaa	Xaa
1				5					10					15	
Pro	Xaa	Pro	Xaa	Xaa	Asp	Phe	Xaa	Asn	25	Leu	Asn	Xaa	Glu	Asp	Xaa
				20										30	
Ile	Leu	Met	Xaa	Xaa	Asn	Leu	Arg	Xaa	Xaa	Asn	Leu	Glu	Ala	Phe	Xaa
				35										45	
Arg	Xaa	Xaa	Lys	Xaa	Xaa	Xaa	Asn	Ala	Ser	Ala	Ile	Glu	Xaa	Xaa	Leu
				50										60	
Xaa	Xaa	Leu	Xaa	Pro	Cys	Leu	Pro	Xaa	Xaa	Thr	Ala	Xaa	Pro	Xaa	Arg
				70										80	
Xaa	Pro	Ile	Xaa	Xaa	Xaa	Xaa	Gly	Asp	Trp	Xaa	Glu	Phe	Xaa	Xaa	Lys
				85										95	
Leu	Xaa	Phe	Tyr	Leu	Xaa	Xaa	Leu	Glu	Xaa	Xaa	Xaa	Xaa	Gln	Gln	
				100										110	

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 133 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 1  
 (D) OTHER INFORMATION: /note= "Met- may or may not precede"



the amino acid in position 1"

- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 18
  - (D) OTHER INFORMATION: /note= "Xaa at position 18 is Asn or Ile"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 19
  - (D) OTHER INFORMATION: /note= "Xaa at position 19 is Met, Ala, or Ile"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 20
  - (D) OTHER INFORMATION: /note= "Xaa at position 20 is Ile, Pro, or Leu"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 23
  - (D) OTHER INFORMATION: /note= "Xaa at position 23 is Ile, Ala, or Leu"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 25
  - (D) OTHER INFORMATION: /note= "Xaa at position 25 is Thr or His"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 29
  - (D) OTHER INFORMATION: /note= "Xaa at position 29 is Gln, Arg, Val, or Ile"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 32
  - (D) OTHER INFORMATION: /note= "Xaa at position 32 is Leu, Ala, Asn, or Arg"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 34
  - (D) OTHER INFORMATION: /note= "Xaa at position 34 is Leu or Ser"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 37
  - (D) OTHER INFORMATION: /note= "Xaa at position 37 is Phe, Pro, or Ser"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 38
  - (D) OTHER INFORMATION: /note= "Xaa at position 38 is Asn or Ala"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 42
  - (D) OTHER INFORMATION: /note= "Xaa at position 42 is Gly, Ala, Ser, Asp, or Asn"

- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 45  
 (D) OTHER INFORMATION: /note= "Xaa at position 45 is Gln,  
 Val, or Met"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 46  
 (D) OTHER INFORMATION: /note= "Xaa at position 46 is Asp  
 or Ser"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 49  
 (D) OTHER INFORMATION: /note= "Xaa at position 49 is Met,  
 Ile, Leu, or Asp"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 50  
 (D) OTHER INFORMATION: /note= "Xaa at position 50 is Glu  
 or Asp"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 51  
 (D) OTHER INFORMATION: /note= "Xaa at position 51 is Asn,  
 Arg, or Ser"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 55  
 (D) OTHER INFORMATION: /note= "Xaa at position 55 is Arg,  
 Leu, or Thr"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 56  
 (D) OTHER INFORMATION: /note= "Xaa at position 56 is Pro  
 or Ser"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 59  
 (D) OTHER INFORMATION: /note= "Xaa at position 59 is Glu  
 or Leu"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 60  
 (D) OTHER INFORMATION: /note= "Xaa at position 60 is Ala  
 or Ser"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 62  
 (D) OTHER INFORMATION: /note= "Xaa at position 62 is Asn  
 Val, or Pro"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 63  
 (D) OTHER INFORMATION: /note= "Xaa at position 63 is Arg  
 or His"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site

- (B) LOCATION: 65
- (D) OTHER INFORMATION: /note= "Xaa at position 65 is Val  
or Ser"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 67
  - (D) OTHER INFORMATION: /note= "Xaa at position 67 is Ser,  
Asn, His, or Gln"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 69
  - (D) OTHER INFORMATION: /note= "Xaa at position 69 is Gln  
or Glu"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 73
  - (D) OTHER INFORMATION: /note= "Xaa at position 73 is Ala  
or Gly"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 76
  - (D) OTHER INFORMATION: /note= "Xaa at position 76 is Ser,  
Ala, or Pro"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 79
  - (D) OTHER INFORMATION: /note= "Xaa at position 79 is Lys,  
Arg, or Ser"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 82
  - (D) OTHER INFORMATION: /note= "Xaa at position 82 is Leu,  
Glu, Val, or Trp"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 85
  - (D) OTHER INFORMATION: /note= "Xaa at position 85 is Leu  
or Val"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 87
  - (D) OTHER INFORMATION: /note= "Xaa at position 87 is Leu,  
Ser, or Tyr"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 88
  - (D) OTHER INFORMATION: /note= "Xaa at position 88 is Ala  
or Trp"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 91
  - (D) OTHER INFORMATION: /note= "Xaa at position 91 is Ala  
or Pro"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 93
  - (D) OTHER INFORMATION: /note= "Xaa at position 93 is Pro"

or Ser"

- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 95
  - (D) OTHER INFORMATION: /note= "Xaa at position 95 is His or Thr"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 98
  - (D) OTHER INFORMATION: /note= "Xaa at position 98 is His, Ile, or Thr"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 100
  - (D) OTHER INFORMATION: /note= "Xaa at position 100 is Lys or Arg"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 101
  - (D) OTHER INFORMATION: /note= "Xaa at position 101 is Asp, Ala, or Met"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 105
  - (D) OTHER INFORMATION: /note= "Xaa at position 105 is Asn or Glu"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 109
  - (D) OTHER INFORMATION: /note= "Xaa at position 109 is Arg, Glu, or Leu"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 112
  - (D) OTHER INFORMATION: /note= "Xaa at position 112 is Thr or Gln"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 116
  - (D) OTHER INFORMATION: /note= "Xaa at position 116 is Lys, Val, Trp, or Ser"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 117
  - (D) OTHER INFORMATION: /note= "Xaa at position 117 is Thr or Ser"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 120
  - (D) OTHER INFORMATION: /note= "Xaa at position 120 is Asn, Gln, or His"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 123
  - (D) OTHER INFORMATION: /note= "Xaa at position 123 is Ala or Glu"

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

```

Ala Pro Met Thr Gln Thr Thr Ser Leu Lys Thr Ser Trp Val Asn Cys
1      5      10      15
Ser Xaa Xaa Xaa Asp Glu Xaa Ile Xaa His Leu Lys Xaa Pro Pro Xaa
20      25      30
Pro Xaa Leu Asp Xaa Xaa Asn Leu Asn Xaa Glu Asp Xaa Xaa Ile Leu
35      40      45
Xaa Xaa Xaa Asn Leu Arg Xaa Xaa Asn Leu Xaa Xaa Phe Xaa Xaa Ala
50      55      60
Xaa Lys Xaa Leu Xaa Asn Ala Ser Xaa Ile Glu Xaa Ile Leu Xaa Asn
65      70      75      80
Leu Xaa Pro Cys Xaa Pro Xaa Xaa Thr Ala Xaa Pro Xaa Arg Xaa Pro
85      90      95
Ile Xaa Ile Xaa Xaa Gly Asp Trp Xaa Glu Phe Arg Xaa Lys Leu Xaa
100     105     110
Phe Tyr Leu Xaa Xaa Leu Glu Xaa Ala Gln Xaa Gln Gln Thr Thr Leu
115     120     125
Ser Leu Ala Ile Phe
130

```

## (2) INFORMATION FOR SEQ ID NO:8:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 111 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (ix) FEATURE:

- (A) NAME/KEY: Modified-site
- (B) LOCATION: 1
- (D) OTHER INFORMATION: /note= "Met- or Met-Ala may or may not precede the amino acid in position 1"

## (ix) FEATURE:

- (A) NAME/KEY: Modified-site
- (B) LOCATION: 4
- (D) OTHER INFORMATION: /note= "Xaa at position 4 is Asn or Ile"

## (ix) FEATURE:

- (A) NAME/KEY: Modified-site
- (B) LOCATION: 5
- (D) OTHER INFORMATION: /note= "Xaa at position 5 is Met, Ala, or Ile"

## (ix) FEATURE:

- (A) NAME/KEY: Modified-site
- (B) LOCATION: 6
- (D) OTHER INFORMATION: /note= "Xaa at position 6 is Ile, Pro, or Leu"

## (ix) FEATURE:

- (A) NAME/KEY: Modified-site
- (B) LOCATION: 9

- (D) OTHER INFORMATION: /note= "Xaa at position 9 is Ile,  
Ala, or Leu"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 11  
(D) OTHER INFORMATION: /note= "Xaa at position 11 is Thr  
or His"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 15  
(D) OTHER INFORMATION: /note= "Xaa at position 15 is Gln,  
Arg, Val, or Ile"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 18  
(D) OTHER INFORMATION: /note= "Xaa at position 18 is Leu,  
Ala, Asn, or Arg"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 20  
(D) OTHER INFORMATION: /note= "Xaa at position 20 is Leu  
or Ser"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 23  
(D) OTHER INFORMATION: /note= "Xaa at position 23 is Phe,  
Pro, or Ser"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 24  
(D) OTHER INFORMATION: /note= "Xaa at position 24 is Asn  
or Ala"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 28  
(D) OTHER INFORMATION: /note= "Xaa at position 28 is Gly,  
Ala, Ser, Asp, or Asn"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 31  
(D) OTHER INFORMATION: /note= "Xaa at position 31 is Gln,  
Val, or Met"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 32  
(D) OTHER INFORMATION: /note= "Xaa at position 32 is Asp  
or Ser"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 35  
(D) OTHER INFORMATION: /note= "Xaa at position 35 is Met,  
Ile, or Asp"
- (ix) FEATURE:  
(A) NAME/KEY: Modified-site  
(B) LOCATION: 36  
(D) OTHER INFORMATION: /note= "Xaa at position 36 is Glu  
or Asp"

- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 37  
 (D) OTHER INFORMATION: /note= "Xaa at position 37 is Asn,  
 Arg, or Ser"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 41  
 (D) OTHER INFORMATION: /note= "Xaa at position 41 is Arg,  
 Leu, or Thr"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 42  
 (D) OTHER INFORMATION: /note= "Xaa at position 42 is Pro  
 or Ser"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 45  
 (D) OTHER INFORMATION: /note= "Xaa at position 45 is Glu  
 or Leu"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 46  
 (D) OTHER INFORMATION: /note= "Xaa at position 46 is Ala  
 or Ser"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 48  
 (D) OTHER INFORMATION: /note= "Xaa at position 48 is Asn,  
 Val, or Pro"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 49  
 (D) OTHER INFORMATION: /note= "Xaa at position 49 is Arg  
 or His"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 51  
 (D) OTHER INFORMATION: /note= "Xaa at position 51 is Val  
 or Ser"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 53  
 (D) OTHER INFORMATION: /note= "Xaa at position 53 is Ser,  
 Asn, His, or Gln"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 55  
 (D) OTHER INFORMATION: /note= "Xaa at position 55 is Gln  
 or Glu"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 59  
 (D) OTHER INFORMATION: /note= "Xaa at position 59 is Ala  
 or Gly"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site

- (B) LOCATION: 62
- (D) OTHER INFORMATION: /note= "Xaa at position 62 is Ser, Ala, or Pro"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 65
  - (D) OTHER INFORMATION: /note= "Xaa at position 65 is Lys, Arg, or Ser"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 67
  - (D) OTHER INFORMATION: /note= "Xaa at position 67 is Leu, Glu, or Val"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 68
  - (D) OTHER INFORMATION: /note= "Xaa at position 68 is Leu, Glu, Val, or Trp"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 71
  - (D) OTHER INFORMATION: /note= "Xaa at position 71 is Leu or Val"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 73
  - (D) OTHER INFORMATION: /note= "Xaa at position 73 is Leu, Ser, or Tyr"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 74
  - (D) OTHER INFORMATION: /note= "Xaa at position 74 is Ala or Trp"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 77
  - (D) OTHER INFORMATION: /note= "Xaa at position 77 is Ala or Pro"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 79
  - (D) OTHER INFORMATION: /note= "Xaa at position 79 is Pro or Ser"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 81
  - (D) OTHER INFORMATION: /note= "Xaa at position 81 is His or Thr"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 84
  - (D) OTHER INFORMATION: /note= "Xaa at position 84 is His, Ile, or Thr"
- (ix) FEATURE:
  - (A) NAME/KEY: Modified-site
  - (B) LOCATION: 86
  - (D) OTHER INFORMATION: /note= "Xaa at position 86 is Lys"



or Arg"

- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 87  
 (D) OTHER INFORMATION: /note= "Xaa at position 87 is Asp, Ala, or Met"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 91  
 (D) OTHER INFORMATION: /note= "Xaa at position 91 is Asn or Glu"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 95  
 (D) OTHER INFORMATION: /note= "Xaa at position 95 is Arg, Glu, or Leu"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 98  
 (D) OTHER INFORMATION: /note= "Xaa at position 98 is Thr or Gln"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 102  
 (D) OTHER INFORMATION: /note= "Xaa at position 102 is Lys, Val, Trp, or Ser"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 103  
 (D) OTHER INFORMATION: /note= "Xaa at position 103 is Thr or Ser"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 106  
 (D) OTHER INFORMATION: /note= "Xaa at position 106 is Asn, Gln, or His"
- (ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 109  
 (D) OTHER INFORMATION: /note= "Xaa at position 109 is Ala or Glu"
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:
- |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asn | Cys | Ser | Xaa | Xaa | Xaa | Asp | Glu | Xaa | Ile | Xaa | His | Leu | Lys | Xaa | Pro |
| 1   |     |     | 5   |     |     |     |     | 10  |     |     |     |     |     | 15  |     |
| Pro | Xaa | Pro | Xaa | Leu | Asp | Xaa | Xaa | Asn | Xaa | Glu | Asp | Xaa | Xaa |     |     |
|     |     | 20  |     |     |     |     | 25  |     |     |     |     |     | 30  |     |     |
| Ile | Leu | Xaa | Xaa | Xaa | Asn | Leu | Arg | Xaa | Xaa | Asn | Leu | Xaa | Xaa | Phe | Xaa |
|     |     | 35  |     |     |     |     | 40  |     |     |     | 45  |     |     |     |     |
| Xaa | Ala | Xaa | Lys | Xaa | Leu | Xaa | Asn | Ala | Ser | Xaa | Ile | Glu | Xaa | Ile | Leu |
|     | 50  |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |     |
| Xaa | Asn | Xaa | Xaa | Pro | Cys | Xaa | Pro | Xaa | Xaa | Thr | Ala | Xaa | Pro | Xaa | Arg |
| 65  |     |     |     | 70  |     |     |     |     |     | 75  |     |     |     | 80  |     |

Xaa Pro Ile Xaa Ile Xaa Xaa Gly Asp Trp Xaa Glu Phe Arg Xaa Lys  
                   85                  90                  95  
 Leu Xaa Phe Tyr Leu Xaa Xaa Leu Glu Xaa Ala Gln Xaa Gln Gln  
                   100                  105                  110

## (2) INFORMATION FOR SEQ ID NO:9:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 111 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro  
 1                  5                  10                  15  
 Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Ala Glu Asp Val Asp  
                   20                  25                  30  
 Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn  
                   35                  40                  45  
 Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu  
                   50                  55                  60  
 Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg  
 65                  70                  75                  80  
 His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys  
                   85                  90                  95  
 Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln  
                   100                  105                  110

## (2) INFORMATION FOR SEQ ID NO:10:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 111 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro  
 1                  5                  10                  15  
 Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp Met Asp  
                   20                  25                  30  
 Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn  
                   35                  40                  45  
 Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu  
                   50                  55                  60  
 Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg  
 65                  70                  75                  80

His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys  
                                   85                                  90                                  95  
 Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln  
                                   100                                  105                                  110

## (2) INFORMATION FOR SEQ ID NO:11:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 111 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Val Pro  
 1                                  5                                  10                                  15  
 Pro Ala Pro Leu Leu Asp Ser Asn Asn Leu Asn Ser Glu Asp Met Asp  
                                   20                                  25                                  30  
 Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn  
                                   35                                  40                                  45  
 Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu  
                                   50                                  55                                  60  
 Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg  
 65                                  70                                  75                                  80  
 His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys  
                                   85                                  90                                  95  
 Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln  
                                   100                                  105                                  110

## (2) INFORMATION FOR SEQ ID NO:12:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 111 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro  
 1                                  5                                  10                                  15  
 Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp  
                                   20                                  25                                  30  
 Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Leu Ala Phe Val  
                                   35                                  40                                  45  
 Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Ala Ile Glu Ser Ile Leu  
                                   50                                  55                                  60  
 Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg

65		70		75		80
His Pro Ile His	Ile Lys Asp Gly Asp Trp	Asn Glu Phe Arg Arg Lys				
	85		90		95	
Leu Thr Phe Tyr	Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln					
	100		105		110	

## (2) INFORMATION FOR SEQ ID NO:13:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 111 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro		
1	5	10
Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp		
	20	25
Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val		
	35	40
Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Ala Ile Glu Ser Ile Leu		
	50	55
Lys Asn Ser Asn Met Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg		
65	70	75
His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys		
	85	90
Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln		
	100	105
		110

## (2) INFORMATION FOR SEQ ID NO:14:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 111 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro		
1	5	10
Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp		
	20	25
Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe Val		
	35	40
Arg Ala Val Lys His Leu Glu Asn Ala Ser Ala Ile Glu Ser Ile Leu		
	50	55
		60

Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg  
 65 70 75 80  
 His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys  
 85 90 95  
 Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln  
 100 105 110

## (2) INFORMATION FOR SEQ ID NO:15:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 111 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro  
 1 5 10 15  
 Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp  
 20 25 30  
 Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn  
 35 40 45  
 Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly Ile Glu Ala Ile Leu  
 50 55 60  
 Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg  
 65 70 75 80  
 His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Arg Lys  
 85 90 95  
 Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln  
 100 105 110

## (2) INFORMATION FOR SEQ ID NO:16:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 111 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro  
 1 5 10 15  
 Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp  
 20 25 30  
 Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn  
 35 40 45  
 Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly Ile Glu Ala Ile Leu  
 50 55 60

Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg  
 65 70 75 80  
 His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Arg Lys  
 85 90 95  
 Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln  
 100 105 110

## (2) INFORMATION FOR SEQ ID NO:17:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 111 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro  
 1 5 10 15  
 Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp  
 20 25 30  
 Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn  
 35 40 45  
 Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu  
 50 55 60  
 Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg  
 65 70 75 80  
 His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Glu Lys  
 85 90 95  
 Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln  
 100 105 110

## (2) INFORMATION FOR SEQ ID NO:18:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 111 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro  
 1 5 10 15  
 Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp  
 20 25 30  
 Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn  
 35 40 45  
 Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu

```

      50              55              60
Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg
65              70              75              80
His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Glu Lys
      85              90              95
Leu Thr Phe Tyr Leu Val Ser Leu Glu His Ala Gln Glu Gln Gln
      100             105             110

```

## (2) INFORMATION FOR SEQ ID NO:19:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 111 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

```

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro
1              5              10              15
Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp
      20              25              30
Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn
      35              40              45
Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly Ile Glu Ala Ile Leu
      50              55              60
Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg
65              70              75              80
His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys
      85              90              95
Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln
      100             105             110

```

## (2) INFORMATION FOR SEQ ID NO:20:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 111 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

```

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro
1              5              10              15
Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp
      20              25              30
Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn
      35              40              45

```

```

Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly Ile Glu Ala Ile Leu
 50                      55                      60
Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Pro Ser Arg
65                      70                      75                      80
His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys
                        85                      90                      95
Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln
100                      105                      110

```

## (2) INFORMATION FOR SEQ ID NO:21:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 111 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

```

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro
 1                      5                      10                      15
Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp
20                      25                      30
Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn
35                      40                      45
Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly Ile Glu Ala Ile Leu
50                      55                      60
Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg
65                      70                      75                      80
His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys
85                      90                      95
Leu Thr Phe Tyr Leu Val Ser Leu Glu His Ala Gln Glu Gln Gln
100                      105                      110

```

## (2) INFORMATION FOR SEQ ID NO:22:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 111 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

```

Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro
 1                      5                      10                      15
Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Ala Glu Asp Val Asp
20                      25                      30
Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val
35                      40                      45

```



185

```

Arg  Ala  Val  Lys  Asn  Leu  Glu  Asn  Ala  Ser  Ala  Ile  Glu  Ser  Ile  Leu
 50                                55                                60

Lys  Asn  Leu  Leu  Pro  Cys  Leu  Pro  Leu  Ala  Thr  Ala  Ala  Pro  Thr  Arg
65                                70                                75                                80

His  Pro  Ile  His  Ile  Lys  Asp  Gly  Asp  Trp  Asn  Glu  Phe  Arg  Arg  Lys
                        85                                90                                95

Leu  Thr  Phe  Tyr  Leu  Lys  Thr  Leu  Glu  Asn  Ala  Gln  Ala  Gln  Gln
      100                                105                                110

```

## (2) INFORMATION FOR SEQ ID NO:23:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 111 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

```

Asn  Cys  Ser  Ile  Met  Ile  Asp  Glu  Ile  Ile  His  His  Leu  Lys  Arg  Pro
 1                                5                                10                                15

Pro  Asn  Pro  Leu  Leu  Asp  Pro  Asn  Asn  Leu  Asn  Ser  Glu  Asp  Met  Asp
      20                                25                                30

Ile  Leu  Met  Glu  Arg  Asn  Leu  Arg  Thr  Pro  Asn  Leu  Leu  Ala  Phe  Val
      35                                40                                45

Arg  Ala  Val  Lys  His  Leu  Glu  Asn  Ala  Ser  Ala  Ile  Glu  Ser  Ile  Leu
      50                                55                                60

Lys  Asn  Leu  Leu  Pro  Cys  Leu  Pro  Leu  Ala  Thr  Ala  Ala  Pro  Thr  Arg
65                                70                                75                                80

His  Pro  Ile  His  Ile  Lys  Asp  Gly  Asp  Trp  Asn  Glu  Phe  Arg  Arg  Lys
      85                                90                                95

Leu  Thr  Phe  Tyr  Leu  Lys  Thr  Leu  Glu  Asn  Ala  Gln  Ala  Gln  Gln
      100                                105                                110

```

## (2) INFORMATION FOR SEQ ID NO:24:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 111 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

```

Asn  Cys  Ser  Ile  Met  Ile  Asp  Glu  Ile  Ile  His  His  Leu  Lys  Val  Pro
 1                                5                                10                                15

Pro  Ala  Pro  Leu  Leu  Asp  Ser  Asn  Asn  Leu  Asn  Ser  Glu  Asp  Met  Asp
      20                                25                                30

Ile  Leu  Met  Glu  Arg  Asn  Leu  Arg  Leu  Pro  Asn  Leu  Leu  Ala  Phe  Val

```

186

```

          35              40              45
Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Ala Ile Glu Ser Ile Leu
 50              55              60
Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg
65              70              75              80
His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys
          85              90              95
Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln
          100              105              110

```

## (2) INFORMATION FOR SEQ ID NO:25:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 113 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

```

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys
 1              5              10              15
Gln Pro Pro Leu Pro Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp
20              25              30
Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala
35              40              45
Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly Ile Glu Ala
50              55              60
Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
65              70              75              80
Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
          85              90              95
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
          100              105              110
Gln

```

## (2) INFORMATION FOR SEQ ID NO:26:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 113 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

```

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys
 1              5              10              15

```

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp  
 20 25 30  
 Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala  
 35 40 45  
 Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly Ile Glu Ala  
 50 55 60  
 Ile Leu Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro  
 65 70 75 80  
 Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg  
 85 90 95  
 Glu Lys Leu Thr Phe Tyr Leu Val Ser Leu Glu Gln Ala Gln Glu Gln  
 100 105 110  
 Gln

## (2) INFORMATION FOR SEQ ID NO:27:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 113 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys  
 1 5 10 15  
 Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp  
 20 25 30  
 Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala  
 35 40 45  
 Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly Ile Glu Ala  
 50 55 60  
 Ile Leu Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro  
 65 70 75 80  
 Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg  
 85 90 95  
 Glu Lys Leu Thr Phe Tyr Leu Val Ser Leu Glu His Ala Gln Glu Gln  
 100 105 110  
 Gln

## (2) INFORMATION FOR SEQ ID NO:28:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 113 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

```

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
 1           5           10           15
Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Ala Glu Asp
          20           25           30
Val Asp Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
          35           40           45
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Ala Ile Glu Ser
          50           55           60
Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro
65           70           75           80
Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg
          85           90           95
Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln
          100          105          110
Gln

```

## (2) INFORMATION FOR SEQ ID NO:29:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 113 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

```

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
 1           5           10           15
Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp
          20           25           30
Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala
          35           40           45
Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Ala Ile Glu Ser
          50           55           60
Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro
65           70           75           80
Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg
          85           90           95
Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln
          100          105          110
Gln

```

## (2) INFORMATION FOR SEQ ID NO:30:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 113 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

```
Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
 1           5           10           15
Val Pro Pro Ala Pro Leu Leu Asp Ser Asn Asn Leu Asn Ser Glu Asp
          20           25           30
Met Asp Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Leu Ala
 35           40           45
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Ala Ile Glu Ser
 50           55           60
Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro
 65           70           75           80
Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg
          85           90           95
Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln
          100          105          110
Gln
```

(2) INFORMATION FOR SEQ ID NO:31:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 113 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

```
Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
 1           5           10           15
Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Ala Glu Asp
          20           25           30
Val Asp Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
 35           40           45
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala
 50           55           60
Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
 65           70           75           80
Ser Arg His Pro Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
          85           90           95
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
```

100

105

110

Gln

## (2) INFORMATION FOR SEQ ID NO:32:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 113 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

```

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
 1           5           10           15
Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp
          20           25           30
Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala
 35           40           45
Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala
 50           55           60
Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
 65           70           75
Ser Arg His Pro Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
          85           90           95
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
      100           105           110

```

Gln

## (2) INFORMATION FOR SEQ ID NO:33:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 113 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

```

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
 1           5           10           15
Val Pro Pro Ala Pro Leu Leu Asp Ser Asn Asn Leu Asn Ser Glu Asp
          20           25           30
Met Asp Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Leu Ala
 35           40           45
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala
 50           55           60

```

```

Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
65              70              75              80
Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
              85              90              95
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
100              105              110
Gln

```

## (2) INFORMATION FOR SEQ ID NO:34:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 113 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

```

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
1              5              10              15
Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Ala Glu Asp
20              25              30
Val Asp Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
35              40              45
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala
50              55              60
Ile Leu Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
65              70              75              80
Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
              85              90              95
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
100              105              110
Gln

```

## (2) INFORMATION FOR SEQ ID NO:35:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 113 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

```

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
1              5              10              15
Val Pro Pro Ala Pro Leu Leu Asp Ser Asn Asn Leu Asn Ser Glu Asp
20              25              30

```

```

Met Asp Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Leu Ala
  35                                40                                45

Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala
  50                                55                                60

Ile Leu Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
  65                                70                                75                                80

Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
  85                                90                                95

Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
  100                                105                                110

Gln

```

## (2) INFORMATION FOR SEQ ID NO:36:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 113 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

```

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
  1                                5                                10                                15

Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp
  20                                25                                30

Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala
  35                                40                                45

Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala
  50                                55                                60

Ile Leu Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
  65                                70                                75                                80

Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
  85                                90                                95

Glu Lys Leu Thr Phe Tyr Leu Val Ser Leu Glu His Ala Gln Glu Gln
  100                                105                                110

Gln

```

## (2) INFORMATION FOR SEQ ID NO:37:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 113 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide



## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys  
 1 5 10 15  
 Val Pro Pro Ala Pro Leu Leu Asp Ser Asn Asn Leu Asn Ser Glu Asp  
 20 25 30  
 Met Asp Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Leu Ala  
 35 40 45  
 Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala  
 50 55 60  
 Ile Leu Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro  
 65 70 75 80  
 Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg  
 85 90 95  
 Glu Lys Leu Thr Phe Tyr Leu Val Ser Leu Glu His Ala Gln Glu Gln  
 100 105 110  
 Gln

## (2) INFORMATION FOR SEQ ID NO:38:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 113 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys  
 1 5 10 15  
 Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp  
 20 25 30  
 Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala  
 35 40 45  
 Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala  
 50 55 60  
 Ile Leu Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro  
 65 70 75 80  
 Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg  
 85 90 95  
 Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln  
 100 105 110  
 Gln

## (2) INFORMATION FOR SEQ ID NO:39:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 113 amino acids

(B) TYPE: amino acid  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

```
Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
 1           5           10           15
Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Ala Glu Asp
          20           25           30
Val Asp Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
          35           40           45
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala
          50           55           60
Ile Leu Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
          65           70           75           80
Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
          85           90           95
Glu Lys Leu Thr Phe Tyr Leu Val Ser Leu Glu His Ala Gln Glu Gln
          100          105          110
Gln
```

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 113 amino acids  
(B) TYPE: amino acid  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

```
Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
 1           5           10           15
Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Ala Glu Asp
          20           25           30
Val Asp Ile Leu Met Asp Arg Asn Leu Arg Leu Ser Asn Leu Glu Ser
          35           40           45
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala
          50           55           60
Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
          65           70           75           80
Ser Arg His Pro Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
          85           90           95
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
          100          105          110
```

Gln

## (2) INFORMATION FOR SEQ ID NO:41:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 113 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

```

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ala Ile His His Leu Lys
 1           5           10           15
Arg Pro Pro Ala Pro Ser Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp
          20           25           30
Met Ser Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
          35           40           45
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala
          50           55           60
Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
65           70           75           80
Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
          85           90           95
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
          100          105          110

```

Gln

## (2) INFORMATION FOR SEQ ID NO:42:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 113 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

```

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
 1           5           10           15
Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp
          20           25           30
Met Ser Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
          35           40           45
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala
          50           55           60
Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
65           70           75           80

```

Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg  
85 90 95

Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln  
100 105 110

Gln

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 113 amino acids  
(B) TYPE: amino acid  
(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

[illegible]

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:

- SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 113 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

Met	Ala	Asn	Cys	5	Ser	Ile	Met	Ile	Asp	10	Glu	Ile	Ile	His	His	Leu	Lys
Arg	Pro	Pro	Ala	20	Pro	Leu	Leu	Asp	25	Pro	Asn	Asn	Leu	Asn	Asp	Glu	Asp
Val	Ser	Ile	Leu		Met	Glu	Arg	Asn	Leu	Arg	Leu	Pro	Asn	Leu	Glu	Ser	

```

          35              40              45
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala
 50              55              60
Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
65              70              75              80
Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
          85              90              95
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
 100              105              110
Gln

```

## (2) INFORMATION FOR SEQ ID NO:45:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 113 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

```

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
 1              5              10              15
Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp
 20              25              30
Met Ser Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
 35              40              45
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala
 50              55              60
Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
65              70              75              80
Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
          85              90              95
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
 100              105              110
Gln

```

## (2) INFORMATION FOR SEQ ID NO:46:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 125 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

```

Met Ala Tyr Pro Glu Thr Asp Tyr Lys Asp Asp Asp Asp Lys Asn Cys
1          5          10
Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala
          20          25          30
Pro Leu Leu Asp Pro Asn Asn Leu Asn Ala Glu Asp Val Asp Ile Leu
          35          40          45
Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala
          50          55          60
Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn
65          70          75          80
Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro
          85          90          95
Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr
          100          105          110
Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln
          115          120          125

```

## (2) INFORMATION FOR SEQ ID NO:47:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 125 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

```

Met Ala Tyr Pro Glu Thr Asp Tyr Lys Asp Asp Asp Asp Lys Asn Cys
1          5          10
Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Asn
          20          25          30
Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu
          35          40          45
Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe Val Arg Ala
          50          55          60
Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn
65          70          75          80
Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro
          85          90          95
Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr
          100          105          110
Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln
          115          120          125

```

## (2) INFORMATION FOR SEQ ID NO:48:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 113 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

```
Met Ala Asn Cys Ser Ile Met Ile Asp Glu Leu Ile His His Leu Lys
 1             5             10             15
Ile Pro Pro Asn Pro Ser Leu Asp Ser Ala Asn Leu Asn Ser Glu Asp
          20             25
Val Ser Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala
      35             40             45
Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala
      50             55             60
Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
 65             70             75             80
Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
      85             90             95
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
      100             105             110
Gln
```

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 134 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

```
Met Ala Pro Met Thr Gln Thr Thr Ser Leu Lys Thr Ser Trp Val Asn
 1             5             10             15
Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro
      20             25             30
Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile
      35             40             45
Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg
      50             55             60
Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys
 65             70             75             80
Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His
      85             90             95
Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu
      100             105             110
Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Thr Thr
      115             120             125
```

Leu Ser Leu Ala Ile Phe  
130

(2) INFORMATION FOR SEQ ID NO:50:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 36 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: other nucleic acid
  - (A) DESCRIPTION: /desc = "synthetic DNA"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

CATGGCAAGA TCTCGGCCA GAATGGAGCT GACTGA

36

(2) INFORMATION FOR SEQ ID NO:51:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 34 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: other nucleic acid
  - (A) DESCRIPTION: /desc = "synthetic DNA"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

AATAGCTGAA TTCTTACCCT TCCTGAGACA GATT

34

(2) INFORMATION FOR SEQ ID NO:52:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 45 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: other nucleic acid
  - (A) DESCRIPTION: /desc = "synthetic DNA"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

ACGTCCATGG CNTCNCNGC NCCNCCTGCT TGTGACCTCC GAGTC

45

(2) INFORMATION FOR SEQ ID NO:53:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 33 base pairs
  - (B) TYPE: nucleic acid



(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid  
(A) DESCRIPTION: /desc = "synthetic DNA"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

TGACAAGCTT ACCTGACGCA GAGGGTGGAC CCT 33

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 465 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: double  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

ATGGCGTCTC CGGCGCCGCC TGCTTGTGAC CTCGAGTCC TCAGTAAACT GCTTCGTGAC	60
TCCCATGTCC TTCACAGCAG ACTGAGCCAG TGCCAGAGG TTCACCCCTT GCCTACACCT	120
GTCTGTCTGC CTGCTGTGGA CTTTAGCTTG GGAGAATGGA AAACCCAGAT GGAGGAGACC	180
AAGGCACAGG ACATTCTGGG AGCAGTGACC CTTCTGCTGG AGGGAGTGAT GGCAGCACGG	240
GGACAACCTGG GACCCACTTG CCTCTCATCC CTCCTGGGGC AGCTTTCTGG ACAGGTCCGT	300
CTCTCTCTTG GGGCCCTGCA GAGCCTCCTT GGAACCCAGC TTCCTCCACA GGCAGGAGACC	360
ACAGCTCACA AGGATCCCAA TGCCATCTTC CTGAGCTTCC AACACCTGCT CCGAGGAAAG	420
GTGCGTTTCC TGATGCTTGT AGGAGGGTCC ACCCTCTGCG TCAGG	465

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 353 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

Met Glu Leu Thr Glu Leu Leu Leu Val Met Leu Leu Thr Ala	
1 5 10 15	
Arg Leu Thr Leu Ser Ser Pro Ala Pro Pro Ala Cys Asp Leu Arg Val	
20 25 30	
Leu Ser Lys Leu Leu Arg Asp Ser His Val Leu His Ser Arg Leu Ser	
35 40 45	

Gln Cys Pro Glu Val His Pro Leu Pro Thr Pro Val Leu Leu Pro Ala  
 50 55 60  
 Val Asp Phe Ser Leu Gly Glu Trp Lys Thr Gln Met Glu Glu Thr Lys  
 65 70 75 80  
 Ala Gln Asp Ile Leu Gly Ala Val Thr Leu Leu Leu Glu Gly Val Met  
 85 90 95  
 Ala Ala Arg Gly Gln Leu Gly Pro Thr Cys Leu Ser Ser Leu Leu Gly  
 100 105 110  
 Gln Leu Ser Gly Gln Val Arg Leu Leu Gly Ala Leu Gln Ser Leu  
 115 120 125  
 Leu Gly Thr Gln Leu Pro Pro Gln Gly Arg Thr Thr Ala His Lys Asp  
 130 135 140  
 Pro Asn Ala Ile Phe Leu Ser Phe Gln His Leu Leu Arg Gly Lys Val  
 145 150 155 160  
 Arg Phe Leu Met Leu Val Gly Gly Ser Thr Leu Cys Val Arg Arg Ala  
 165 170 175  
 Pro Pro Thr Thr Ala Val Pro Ser Arg Thr Ser Leu Val Leu Thr Leu  
 180 185 190  
 Asn Glu Leu Pro Asn Arg Thr Ser Gly Leu Leu Glu Thr Asn Phe Thr  
 195 200 205  
 Ala Ser Ala Arg Thr Thr Gly Ser Gly Leu Leu Lys Trp Gln Gln Gly  
 210 215 220  
 Phe Arg Ala Lys Ile Pro Gly Leu Leu Asn Gln Thr Ser Arg Ser Leu  
 225 230 235 240  
 Asp Gln Ile Pro Gly Tyr Leu Asn Arg Ile His Glu Leu Leu Asn Gly  
 245 250 255  
 Thr Arg Gly Leu Phe Pro Gly Pro Ser Arg Arg Thr Leu Gly Ala Pro  
 260 265 270  
 Asp Ile Ser Ser Gly Thr Ser Asp Thr Gly Ser Leu Pro Pro Asn Leu  
 275 280 285  
 Gln Pro Gly Tyr Ser Pro Ser Pro Thr His Pro Pro Thr Gly Gln Tyr  
 290 295 300  
 Thr Leu Phe Pro Leu Pro Pro Thr Leu Pro Thr Pro Val Val Gln Leu  
 305 310 315 320  
 His Pro Leu Leu Pro Asp Pro Ser Ala Pro Thr Pro Thr Pro Thr Ser  
 325 330 335  
 Pro Leu Leu Asn Thr Ser Tyr Thr His Ser Gln Asn Leu Ser Gln Glu  
 340 345 350  
 Gly

## (2) INFORMATION FOR SEQ ID NO:56:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 174 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

```

Met Glu Leu Thr Glu Leu Leu Leu Val Val Met Leu Leu Leu Thr Ala
 1           5           10
Arg Leu Thr Leu Ser Ser Pro Ala Pro Ala Cys Asp Leu Arg Val
 20          25          30
Leu Ser Lys Leu Leu Arg Asp Ser His Val Leu His Ser Arg Leu Ser
 35          40          45
Gln Cys Pro Glu Val His Pro Leu Pro Thr Pro Val Leu Leu Pro Ala
 50          55          60
Val Asp Phe Ser Leu Gly Glu Trp Lys Thr Gln Met Glu Glu Thr Lys
 65          70          75          80
Ala Gln Asp Ile Leu Gly Ala Val Thr Leu Leu Leu Glu Gly Val Met
 85          90          95
Ala Ala Arg Gly Gln Leu Gly Pro Thr Cys Leu Ser Ser Leu Leu Gly
100         105         110
Gln Leu Ser Gly Gln Val Arg Leu Leu Gly Ala Leu Gln Ser Leu
115         120         125
Leu Gly Thr Gln Leu Pro Pro Gln Gly Arg Thr Thr Ala His Lys Asp
130         135         140
Pro Asn Ala Ile Phe Leu Ser Phe Gln His Leu Leu Arg Gly Lys Val
145         150         155         160
Arg Phe Leu Met Leu Val Gly Gly Ser Thr Leu Cys Val Arg
165         170

```

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1059 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

```

ATGGAGCTGA CTGAATTGCT CCTCGTGGTC ATGCTTCTCC TAACTGCAAG GCTAACGCTG      60
TCCAGCCCGG CTCCTCCTGC TTGTGACCTC CGAGTCCTCA GTAAACTGCT TCGTGACTCC      120
CATGTCTTTC ACAGCAGACT GAGCCAGTGC CCAGAGGTTC ACCCTTTGCC TACACCTGTC      180
CTGCTGCCTG CTGTGGACTT TAGCTTGGGA GAATGGAAAA CCCAGATGGA GGAGACCAAG      240
GCACAGGACA TTCTGGGAGC AGTGACCTTT CTGCTGGAGG GAGTGATGGC AGCACGGGGA      300

```

CAACTGGGAC CCACTTGCTC CTCATCCCTC CTGGGGCAGC TTTCTGGACA GGTCCGTCTC	360
CTCCTTGGGG CCCTGCAGAG CCTCCTTGGA ACCCAGCTTC CTCACAGGG CAGGACCACA	420
GCTCACAAGG ATCCCAATGC CATCTTCCTG AGCTTCCAAC ACCTGCTCCG AGGAAAGGTG	480
CGTTTCCTGA TGCTTGTAGG AGGGTCCACC CTCTGCCTCA GCGGGGCCCC ACCCACCACA	540
GCTGTCCCA GCAGAACCTC TCTAGTCTC ACCTGAACG AGCTCCCAA CAGGACTTCT	600
GGATTGTTGG AGACAACTT CACTGCCTCA GCCAGAACTA CTGGCTCTGG GCTTCTGAAG	660
TGGCAGCAGG GATTGAGAG CAAGATTCTT GGTCTGCTGA ACCAAACCTC CAGGTCCCTG	720
GACCAAAATCC CCGGATACCT GAACAGGATA CACGAACTCT TGAATGGAAC TCGTGGACTC	780
TTTCCTGGAC CCTCACGAG GACCCTAGGA GCCCCGACA TTTCCTCAGG AACATCAGAC	840
ACAGGCTCCC TGCCACCCAA CCTCCAGCCT GGATATTCTC CTTCCCAAC CCATCTCCT	900
ACTGGACAGT ATACGCTCTT CCCTCTTCCA CCCACCTTGC CCACCCCTGT GGTCCAGCTC	960
CACCCCTGCT TCTCTGACCC TTCTGTCTCA ACGCCACCC CTACCAGCCC TCTTCTAAAC	1020
ACATCTTACA CCACTCCCA GAATCTGTCT CAGGAAGGG	1059

## (2) INFORMATION FOR SEQ ID NO:58:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 408 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA other nucleic acid

(A) DESCRIPTION: /desc = "synthetic DNA"

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

ATGGCTCCAA TGACTCAGAC TACTTCTCTT AAGACTTCTT GGGTTAACTG CTCTAACATG	60
ATCGATGAAG TTATAACACA CTTAAAGCAG CCACCTTTGC CTTTGCTGGA CTTCACAAAC	120
CTCAATGGGG AAGACCAAGA CATTCTGATG GAAAATAACC TTCGAAGGCC AAACCTGGAG	180
GCATTCAACA GGGCTGTCAA GAGTTTACAG AATGCATCAG CAATTGAGAG CATTCTTAAA	240
AATCTCTGCT CATGCTGCCC CCGGCCACG GCCGCACCCA CGCGACATCC AATCCATATC	300
AAGGACGGTG ACTGGAATGA ATTCCGTCGT AAATGACCT TCTATCTGAA AACCTGGAG	360
AACGCGCAGG CTCACAGAG CACTCTGTCG CTAGCGATCT TTTAATAA	408